

**A STUDY OF
MYCOPHENOLATE AND STEROIDS
IN IGA NEPHROPATHY**

A dissertation submitted to the **Tamilnadu Dr.M.G.R. Medical
University, Chennai** in partial fulfillment of D.M. Branch II
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BONAFIDE CERTIFICATE

This is to certify that the work presented in this dissertation titled “**A STUDY OF MYCOPHENOLATE AND STEROIDS IN IGA NEPHROPATHY**” done towards partial fulfillment of the requirements of the Tamil Nadu Dr. M.G.R. Medical University, Chennai for the D.M. (Branch II) (Nephrology) exams to be conducted in July/August 2010, is a bonafide work of the candidate Dr. Satya Vamseedhar.P , Senior Post graduate student in the Department of Nephrology, Christian Medical College, Vellore under my guidance and supervision. This dissertation has not been submitted, fully or in part to any other board or University.

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ABSTRACT

A STUDY OF MYCOPHENOLATE AND STEROIDS IN IGA NEPHROPATHY

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Aim: IgA Nephropathy (IgAN) has a rapid course in the Indian population. This case control study was performed to study mycophenolate (MPA) in high risk IgAN.

Methods: 41 IgAN cases at high risk of progression (24 hour proteinuria >3grams or e GFR(MDRD) <60ml/min/1.73m² or mean arterial pressure (MAP) ≥107mmHg or glomerulosclerosis involving ≥50% of glomeruli) who were treated with MPA (dose controlled with therapeutic drug monitoring) and steroids +/- ACE-I/ARB were compared to two historical control groups, one that received steroids +/- ACE-I/ARB (control 1, n=31) and the other, without immunosuppression +/- ACE-I/ARB (control 2, n=41).

Results: Baseline characteristics of 3 groups were similar with respect to age, sex, MAP, proteinuria whereas e GFR in control 1 was higher by 15 ml/min. (p=0.03). Mann-Whitney test was used. In cases, control 1 and control 2, after 3 months of treatment, median percent change in e GFR was 16.93, 11.62, -8.23, %change in s. creatinine was -12.5, -1.17, -1.32 and %change in proteinuria was -58.76, -45.31 and -48.53 respectively.

When cases were compared to control 2, there was a significant improvement in e GFR and s.creatinine ($p=0.004$ and 0.005) respectively, whereas there was a trend towards improvement in proteinuria in cases by 10% ($p=0.313$). On comparing cases to control 1, there was a trend towards improvement of proteinuria and e GFR in cases by 13% ($p=0.548$) and 5% ($p=0.58$) respectively. Sub group analysis of patients in the 3 groups who received ACE-I/ARB revealed similar trends.

Conclusions: In high risk IgAN patients, MPA+steroids+ACE-I/ARB was beneficial with respect to improvement in renal function when compared to ACE-I/ARB alone and there was a trend towards better renal function when compared to steroids + ACE-I/ARB.

Review of literature

IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis in the developed world and it is an important cause of end stage kidney failure [1,2]

History of IgA Nephropathy (Berger's Disease) –

The idea of using fluorescent-labeled specific antibodies to detect proteins in tissue was introduced by Coons and Kaplan[3] in 1950 and was first used for evaluation of diseased renal tissue by Mellors and Ortega[4] in 1957.

Percutaneous renal biopsy was initially described as a technique to diagnose kidney disease by Iverson and Brun in 1951 [5] .

Tomasi *et al.* had discovered the IgA immune system in 1965 [6].

Thus two techniques, immunofluorescent tagging of antibodies to detect antigens in tissues and percutaneous renal biopsy, along with the discovery of a new immunoglobulin present in serum and in tissue secretions (IgA) all paved the way for the seminal observations , beginning in 1967 of Jean Berger and Nicole Hinglais at the Necker Hospital in Paris, France concerning a new entity they subsequently called mesangial IgA/IgG deposition . They described their novel observations in a brief paper published in 1968 which described predominant IgA mesangial deposition in some renal biopsies where the immunostaining of IgA strongly outshone the IgG reagent. This was the discovery of IgA nephropathy, also subsequently called Berger's disease [7] .

The different names of IgA nephropathy are -

1. Nephropathy with mesangial IgA-IgG deposits
2. Les glomerulopathies primitives a depots mesangiaux d'IgA et d'IgG
3. Diffuse intra- und extrakapillare Glomerulonephritis mit IgA-Depots

4. IgA-IgG-Nephropathie
5. Glomerulites a depots d'IgA diffuse dan le mesangium
6. IgA-associated glomerulonephritis
7. IgA nephropathy
8. IgA-IgG deposits nephritis
9. Immunoglobulin A glomerulonephritis
10. Primary glomerulonephritis with mesangial deposits of IgA
11. Benign hematuria-loin pain syndrome

Epidemiology and Ancestral Difference :

Deposition of IgA is present in 4%–16% of normal, healthy living adults and cadaveric donors , the significance of which is not completely understood . Thus, from the epidemiological perspective, the biopsy-proven IgAN cases represent a very small fraction of the total individuals with such deposits in the population as a whole [8,9] .

In 1988 Levy and Berger outlining the “Worldwide perspective of IgA nephropathy” suggested that the apparent geographic variations in the percentage of this glomerulonephritis in kidney biopsy specimens could reflect different clinical policies for diagnostic tests more than a real ancestral difference [10] .

The systematic screening of urine samples could have influenced the higher prevalence reported both in Japan and in Singapore, the rare detection of IgAN in blacks either from the United States or from Africa was to be ascribed to the infrequent performance of biopsies in African patients with only microscopic hematuria and the frequent absence of immunofluorescence applied to renal biopsy [11 , 12] .

While on one hand they were quite attentive to this primary aspect, they also got the hint that ancestral differences could suggest a possible role of genetic factors in the etiology of IgAN.

The clinical onset of IgAN is usually found in the second and third decade of life but may occur at any age. Males are affected from two-fold in Japan, to six-fold more than females as reported in Europe and in the United States. The disease is more frequent in Whites and Asians than in Blacks from United States and South Africa, but the explanation of this difference is still unknown.

Most of the worldwide studies report prevalence rates as a percentage of cases of primary glomerulonephritides or as a percentage of a total series of renal biopsies, while few epidemiologic studies focused on the real incidence of primary IgAN in various populations [13].

An interesting study by Geddes *et al.* aimed at examining four IgAN databases from four different countries in three continents to determine if geographic variability in long term outcome is independent of renal function, proteinuria and blood pressure at the time of diagnosis. They included patients from Glasgow (United Kingdom), Helsinki (Finland), Sydney (Australia) and Toronto (Canada). The results supported the hypothesis that the variation in the rate of progression of renal disease was probably due to variability at presentation in both duration (lead-time bias) and severity of disease in different countries. They did not exclude the possibility that true geographic variability exists mainly because of genetic variability, but also because of environmental factors, including dietary differences between countries. The geographic variability is responsible for difference in

ten year renal survival in patients with IgAN ranging between 95.7% in Helsinki and 61.6% in Toronto [14].

The role of environmental antigen triggers together with a genetic susceptibility factor determining the onset of the disease is still under debate. The higher prevalence of IgAN in Asian/Pacific Islanders could be supported by the evidence that high intake of rice and n-6 poly-unsaturated fatty acids could be associated with an increased risk of the disease as reported by Wakai *et al.* [161] or by the suggested role of *Hemophilus parainfluenzae* as a causative agent of the disease in Japanese individuals [15 , 16 ,17].

Worldwide Distribution

Europe :

The incidence of IgAN in Italy is 8.4 patients per million population(pmp) per year. According to the Italian Registry of Renal Biopsies (IRRB), based on data related to 32,862 renal biopsies collected during the years 1987–2000 from 128 renal units in Italy, IgAN is the most frequent disease among primary glomerulonephritides (21.5%) and its frequency is higher in males (39.3%) than in females (27.8%) (<http://www.irrb.net>).

The disease is also the most common primary glomerulopathy in Germany.

In a study of renal biopsies between 1970 and 1986, with a sample size of 8545 cases in adults and 1364 in children, Rivera *et al.* described the high incidence of IgAN and the decrease of membranoproliferative glomerulonephritis in Spain. The mean annual incidence (pmp) of the disease was 7.9, making the disease the most common primary nephropathy [18].

America :

In Brazil, IgAN (29.4%) is the most frequent disease diagnosed among non-nephrotic patients. An increase in frequency of focal and segmental glomerulosclerosis has been reported in non-nephrotic patients; thus this disease became as common as IgAN (31.6% and 28.0%, respectively) from 1994–1999 [19] .

The most common primary glomerular disease in San Paolo is focal and segmental glomerulosclerosis (29.7%), followed by membranous nephropathy (20.7%) and IgAN (17.8%), confirming the above data [20] .

The United States Renal Data System (USRDS) reports that 0.8% of incident end stage renal disease patients in the USA have documented or suspected IgAN (<http://www.usrds.org>) .

In a 30-year renal biopsy study in Olmsted County (Minnesota), IgAN was present in 22% of biopsy-proven patients, thus representing the most frequent glomerulonephritis [21].

In 2006, Nair and Walker examined if IgAN still remained the most common primary glomerulopathy among young adults in the USA. In their study from a large renal biopsy referral center serving Midwestern and Southern states they grouped the patients in adults (≥ 20 years) and young adults (20–39 years). The disease was the most common primary glomerulopathy in young adult Caucasians (with a ratio IgAN/focal segmental glomerulosclerosis of 2.1:1) and also the most common cause of end-stage renal disease in this race. On the contrary, the disease was rare in African Americans in whom focal segmental glomerulosclerosis remains more common (focal segmental glomerulosclerosis/IgAN 9.7:1) [22] .

Australia :

In a retrospective review of the pathology reports of all native renal biopsies performed in the state of Victoria, Australia, the most common glomerulonephritis in adults in 1995 and 1997 was IgAN (10.5 per 100,000 individuals). The disease accounted for 34.1% of all biopsy proven glomerulonephritides and was also the most common cause of end-stage renal disease due to glomerulonephritis [23] .

Asia :

Renal biopsy has been routinely performed in China in the last 20 years and IgAN is the most common primary glomerulonephritis occurring in the largest Asian country, representing 45.3% of the primary glomerulonephritides. The disease is also the leading cause of end stage renal disease, accounting for approximately 18% of patients [24 , 25]. It has also been reported at a frequency of 35% in Hong Kong by Lai and 34% in Singapore by Sinniah in the 1980s [26] .

In Korea, in a study on a total of 4514 cases of renal biopsy collected over a 23-year period between 1973 and 1995, the most common primary glomerulonephritis in adults was minimal change disease (26.6%), followed by IgAN (22.1%) [27] .

The disease is listed as the primary cause of end stage renal disease in 28% of new dialysis patients as reported by Koyama *et al.* in a national survey of Japanese patients [28].

The Research Group on Progressive Chronic Renal Disease, in their Nationwide and long-term survey of primary glomerulonephritis in Japan, found that 47.4% of 1045 biopsy specimens examined by immunofluorescence microscopy were IgAN [29].

In a retrospective analysis of 1592 renal biopsies received from various hospitals all over Kerala (India) over a period of two years, Chandrika observed that of the 1544 native kidney biopsies, the majority of cases (18.84%) were focal segmental glomerulosclerosis followed in frequency by IgAN (14.26%) [30] .

Genetic Contribution to IgA Nephropathy :

Several lines of evidence support a contribution by genetic factors to the development of, or susceptibility to, overt IgAN –

1. Many pedigrees have been described in which more than one individual is affected by IgAN. In some of these, genetic loci have been identified by linkage analyses[31,32,33].
2. There are differences in prevalence in ethnically different populations which are unlikely to be fully accounted for by differences in environment and ascertainment [34].
3. First and second degree relatives of IgAN patients have higher relative risks of developing this disease compared to the general population [35].

Most cases of IgAN are “sporadic” rather than familial. IgAN is therefore generally considered to be a complex disorder, i.e. it is a multifactorial disease with both genetic and environmental factors . However, in some families the disease segregates in an obviously autosomal dominant fashion. It therefore seems likely that the genetic contribution to the disease is heterogenous, and can lie anywhere in the spectrum from monogenic, through oligogenic to polygenic.

Using linkage analysis, several loci have been implicated in IgAN in different pedigrees - 2q36 locus, 6q22-q23 (IGAN1) and 3p24-p23 loci, 4q26-q31 (IGAN2) and 17q12-q22 (IGAN3) loci. The relative risk of IgAN is 16 times higher in first degree relatives (parents and siblings), and more than two-fold increased in second degree relatives (grandparents, grandchildren) of index cases compared to the general population [35]. Some genetic variations may contribute to more rapid progression of the disease . There is some evidence that variants in ACE (Angiotensin I converting enzyme I) [36] and AGT (Angiotensinogen) alter response to ACE inhibitors and/or angiotensin receptor blocker [37].

Histopathology, Immunofluorescence and Ultrastructural Examination :

Primary IgAN is a chronic glomerulonephritis defined by the presence or deposition in the mesangium of predominant IgA-C3 immune complexes, within which antigenic moiety remains elusive [38]. IgAN has conventionally been subdivided into primary and secondary IgA nephropathy, depending upon whether there is absence or presence of recognizable systemic conditions, respectively. These systemic diseases refer to Henoch-Schonlein purpura, dermatitis herpetiformis, liver cirrhosis, chronic hepatitis, coeliac disease, ankylosing spondylitis, rheumatoid arthritis, Reiter's syndrome, human immunodeficiency virus infection, mycosis fungoides and lung cancer.

Renal biopsy is necessary to establish the diagnosis of IgAN and also useful in prognostic information it may provide for the management of patient, clinical trials, and for assessing renal survival.

Histopathology of IgA Nephropathy :

There have been many proposed classifications of renal lesions, but none of these is widely adopted. The separation of renal lesions into active and chronic is somewhat arbitrary, in that the pathogenesis of these lesions is poorly understood.

Acute Renal Lesions in IgA Nephropathy :

Mesangial hypercellularity is diagnosed when the mesangial cells exceed three per segmental area to as much as ten or 20 mesangial cells. This lesion is common, with characteristic focal and segmental distribution, particularly in early disease. These may be accompanied by expansion of mesangial matrix or sclerosis. Mesangial hypercellularity is not correlated with disease progression or renal survival [39].

Necrotizing lesion can be defined when any three of the following features are identified in glomeruli - disruption of capillary wall, mesangiolysis, leucocytic infiltration, nuclear fragments, fibrinous deposits or cellular crescents. It is seen in about 10% of patients with IgAN and up to 50% in the nephritis of Henoch-Schonlein purpura. While this lesion may not affect actuarial renal survival, immunosuppression is beneficial to prevent flares and progression to end-stage renal failure in some of the patients [40].

Epithelial hypercellularity forming three or more solid layers constitute a cellular crescent. Some cases may respond to cytotoxic drugs and plasma exchange [41].

In contrast to lupus nephritis, global endocapillary hypercellularity with or without leucocytic infiltration, and interstitial inflammatory cells infiltrates unrelated to tubulo-

interstitial fibrosis are all uncommon. When present, these consist generally of modest focal and segmental lesions in IgAN. These glomerular lesions have not been correlated with disease progression or renal survival.

Chronic Renal Lesions in IgA Nephropathy :

Glomerular sclerosis refers to accumulation of mesangial or basement membrane matrix. Its pathogenesis is incompletely understood, but inflammatory mediators such as TGF- β , PAI-1, and PDGFs play an important role in their development and their progression [42]. The clinical correlation between extent of glomerular sclerosis and loss of renal function supports the notion that sclerosing process is cumulative and parallels the progressive decrease in functional nephrons.

Tubular atrophy and interstitial fibrosis - In part they result from glomerular sclerosis and are regarded as secondary to the primary glomerular injury. There is no evidence of an immune mediated tubular insult as in lupus nephritis, however activated inflammatory mediators and inflammatory cells induced by chronic proteinuria are contributory [43]. In most biopsies however, the extent of tubular atrophy and interstitial fibrosis matches that of glomerulosclerosis, and correlated by semi-quantitative analysis [44]. Three patterns of chronic tubulo-interstitial lesions can be recognized in IgAN. Most commonly, tubular atrophy and interstitial fibrosis appear **diffuse** and parallel the extent of glomerular sclerosis. The second pattern of tubulo-interstitial scarring refers to the so-called “**striped fibrosis**” distribution, which consists of groups of atrophic tubules and advanced glomerular sclerosis, alternating with groups of intact nephrons. It results from hypertensive hyaline arteriosclerosis. The third pattern is uncommon, and may be

recognized when tubular injury appears more pronounced than the extent of glomerular sclerosis, this raises the possibility of a superimposed drug-induced interstitial nephritis.

Hyaline arteriosclerosis is identified in at least a third of the patients with IgAN at the time of biopsy, and is attributed to hypertension.

Immunofluorescence Examination of IgA Nephropathy :

Mesangial deposition of predominant IgA-C3 immune complexes defines the disease[45] and consists mostly of polymeric IgA1 with the absence of secretory component and presence of J chain, regarded as the result of abnormal glycosylation of the IgA1 molecule [46]. Peripheral capillary loop deposits may or may not be found.

Ultrastructural Examination of IgA Nephropathy :

In a majority of patients with IgAN, the findings of electron microscopy do not add to the diagnosis. The salient feature consists of mesangial electron dense deposits (EDDs), which are per se not diagnostic, unless done using immuno-electron microscopy labeling with anti-human IgA and C3 reagents [47]. A particular globular distribution of mesangial or paramesangial EDDs protruding into the urinary space is common in IgAN, but rarely seen in other glomerulonephritis. Truly isolated subendothelial or subepithelial EDDs are observed in 10% to 20% of the cases in the literature [48].

Two or more primary glomerular diseases may co-exist or be overlapping, requiring electron microscopy for diagnosis. Co-existent minimal change nephropathy, membranous nephropathy, diabetic nephropathy and thin membrane nephropathy are recognized.

Tubulointerstitial Injury in IgA Nephropathy :

In IgA nephropathy, several studies have shown that the degree of tubular atrophy and interstitial fibrosis correlate better with deterioration of renal function than the extent of glomerular injury. In a study of 194 patients with a mean follow-up of ten years, tubular grade 2 defined as $\geq 25\%$ but $< 50\%$ tubular damage (relative risk: 5.5) and grade 3 defined as $> 50\%$ tubular damage (relative risk: 28.8) were the best factors to predict chronic renal failure in multivariate analysis [49].

To *et al.* examined separately the degree of glomerulosclerosis, tubulointerstitial damage, and hyaline arteriosclerosis in 126 renal biopsies of IgA nephropathy. In this study, global glomerulosclerosis represented the only independent prognostic factor for renal survival. Both glomerulosclerosis and tubulointerstitial damage, however, were significantly correlated with the degree of proteinuria, hypertension and serum creatinine level [39] .

More recently, Myllymaki *et al.* analyzed 204 renal biopsies of IgA nephropathy and concluded from a multivariate analysis that interstitial fibrosis and tubulointerstitial inflammation were independently associated with progressive disease[50].

In the evidence-based Oxford classification 2008 for IgA nephropathy, tubular atrophy/interstitial fibrosis was significantly associated with renal outcome independently of glomerular filtration rate, proteinuria, and blood pressure at presentation.

Altogether these independent clinicopathological studies reveal that the degree of tubulointerstitial damage correlates with deterioration of renal function in IgA nephropathy.

The principal mechanisms implicated in the progression of tubulointerstitial injury in IgA nephropathy are –

1. Glomerulo-Tubular Communication :

In recent years, glomerulotubular crosstalk has been proposed as one of the mechanisms involved [43]. Upon deposition of IgA, mesangial cells start to proliferate and release cytokines/chemokines, among which TNF- α and IL-6. These inflammatory mediators are filtered by damaged glomeruli and stimulate downstream tubular epithelial cells (TECs), which subsequently produce proinflammatory mediators including IL-1, TNF- α , MIF, IL-8, MCP-1, RANTES, and sICAM-1 [51].

2. Proteinuria :

Proteinuria leads to activation of the nuclear NF- κ B transcription factor in TECs that, in turn, induces the up-regulation of pro-inflammatory cytokines/chemokines including MCP-1, RANTES, and osteopontin but also of the profibrogenic cytokine TGF- β [52].

3. Downstream interstitial fibrosis due to reduced blood supply because of glomerulosclerosis .

4. Misdirected filtration into the interstitium from the synechiae of glomerulosclerotic segments.

5. Leukocytes :

Chemokines play pivotal roles in the recruitment of inflammatory cells into the kidney. The chemokine receptors CXCR3 and CCR5 are expressed on activated T cells. Interstitial CXCR3, as well as CCR5-positive T cells may play a role in the progression of renal diseases [53,54] .

PDGF is a potent chemo-attractant for macrophages. In addition, it causes the release of other cytokines among which TGF- β is predominant. Interstitial PDGFR- β is significantly increased in IgA nephropathy and associated with monocyte/macrophage infiltration [55].

The secretion of cytokines by TECs not only leads to up-regulation of adhesion molecules including ICAM-1 and CD44 but also of MHC class II and the co-stimulatory signals CD80 and CD86, which support infiltration and activation of inflammatory cells. In a study comprising 33 cases of IgA nephropathy, CD80/CD86 expression correlated with renal function at the time of renal biopsy and with monocyte/macrophage infiltration. These data support the hypothesis that TECs in IgA nephropathy may act as antigen presenting cells and activate T cells [56].

In contrast, little has been published about B-cell infiltration and IgA nephropathy. Heller *et al.* characterized B-cell infiltrates and the factors involved in B-cell recruitment in 18 cases of IgA nephropathy. They concluded that CD20-positive B cells form a prominent part of the interstitial inflammatory infiltrate and that B-cell infiltrates are associated with increased local expression of the chemokine CXCL13 and the corresponding receptor CXCR5 on B cells. However, no correlation could be established between B cell infiltration and the Haas classification of IgA nephropathy [57].

6. Growth Factors

Hepatocyte growth factor (HGF) has recently emerged as a potent antifibrotic and reno-protective factor that counteracts the pro-fibrotic actions of TGF- β [58]. This may represent an endogenous mechanism of repair.

The expression of TGF- β is increased in tubules and tubulointerstitial areas in IgA nephropathy and correlates significantly with the severity of histological damage [59]. TGF- β has also been shown to induce the activation of the transcription factor c-Jun in TECs that in turn regulates the expression of genes involved in proliferation and inflammation [60].

Progression of renal disease correlates with rarefaction of the peritubular capillary network which results from an increase in the expression of the anti-angiogenic factor thrombospondin-1 (TSP-1) and decrease of the pro-angiogenic factor vascular endothelial growth factor (VEGF) by tubular epithelial cells[61].

7. Myofibroblast Influx

Accumulation of myofibroblasts in the interstitium is a key event in the development of fibrosis. These cells are characterized by the expression of α -smooth muscle actin (α -SMA) and fibroblastic-specific protein-1(FSP-1) [62]. In a series of 38 patients with IgA nephropathy, the intensity of the interstitial α -SMA staining correlated with renal functional outcome [63].

8. Matrix Metalloproteinases

Accumulation of extracellular matrix (ECM) results from an imbalance between synthesis by myofibroblasts and degradation by matrix metalloproteinases (MMP) [64]. Surprisingly, very few studies address the issue of MMP activity in IgA nephropathy. Brisk glomerular activity of MMP-9 and, to a lesser extent, MMP-2 has been reported in IgA nephropathy [65]. Furthermore, peripheral blood mononuclear cells(PBMCs) from patients with IgA nephropathy have been shown to express higher level of MMP-9 mRNA than those from patients with other forms of glomerulonephritis or from healthy controls [66].Also, MMP-9 mRNA production by PBMCs correlated significantly with the severity of histopathologic grading for IgA according to Haas.

Although these data suggest that PBMC-derived MMP are of importance during disease progression in IgA nephropathy, solid data on MMP activity in the tubulointerstitial compartment in IgA nephropathy are currently lacking.MMP-9 activity can lead to destruction of the tubular basement membrane which in turn results in myofibroblastic transition of TECs via epithelial-mesenchymal transition.

9. The Renin-Angiotensin System

The Renin-Angiotensin system (RAS) has been shown to play a key role in the development of renal fibrosis. While several components of the RAS exert profibrotic activity, Angiotensin II (Ang II), produced by activated macrophages and fibroblasts has been shown to be the key hormone responsible for renal fibrosis [67]. Ang II induces expression of several cytokines/chemokines, including TGF- β , TNF- α , IL-6, MCP-1 and RANTES, through interaction with the Ang II receptors type 1 and 2 (ATR1 and ATR2) [68].

Furthermore, Ang II influences renal tissue turnover by mediating TEC apoptosis (via interaction with ATR2) while at the same time mediating TEC proliferation (via ATR1)[69]. Pharmacologic blockade of the RAS effectively slows down the progression of interstitial fibrosis [70].

In IgA nephropathy, the intrarenal RAS is activated. In a study of 20 renal biopsies from IgA nephropathy patients, mRNA levels of angiotensinogen, renin, ACE and AT1R and AT2R were significantly enhanced in both microdissected glomerular and tubulointerstitial tissue samples [71].

10. CD44

The shortest form of CD44, CD44 standard (CD44s), is able to bind hyaluronan and osteopontin, two major components of the extracellular matrix. CD44 comprises a family of type I transmembrane glycoproteins with a wide tissue distribution that are involved in cell-cell and cell-matrix interactions [72]. Using murine models of renal diseases, it has been shown that CD44 plays a crucial role in the cascade of renal inflammation, tubular

atrophy, rarefaction of the peritubular capillary network and ultimately fibrosis [73].

Under normal conditions, CD44 is undetectable in the kidney except in passenger leukocytes. In IgA nephropathy, a strong basolateral expression of CD44 was observed in damaged tubules as well as in the interstitium. CD44 expression paralleled the degree of tubular atrophy and interstitial fibrosis and correlated significantly with the degree of proteinuria[74].

Podocyte Pathology :

Podocytes are unique epithelial cells necessary for maintaining the selectivity and integrity of the glomerular filtration barrier. Podocytes have also been shown to fully express most or all the elements of the renin-angiotensin system (RAS) [75]. In vitro studies of podocytes cultured with either supernatant from mesangial cells cultured with polymeric IgA isolated from patients with IgA nephropathy (IgAN) or recombinant tumor necrosis factor- α (TNF- α) reveal enhanced proinflammatory changes with increased synthesis of TNF- α and interleukin-6 (IL-6) [76].

Necrosis and detachment of the podocytes from the glomerular basement membrane was observed in IgAN [77]. Complementing the histological findings of podocytopenia, patients with IgAN had increased urinary excretion of podocytes[78]. Treatment with angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist reduced the urinary excretion of podocyte in IgAN [79].

Lai *et al.* examined the expression of two podocyte markers (nephrin and ezrin) in renal biopsy from patients with IgAN with mild histological grading. A reduction in nephrin and ezrin was clearly evident in these patients with mild IgAN. These markers

were examined as nephrin has a crucial role in the filtration barrier of the glomerular podocyte and ezrin is a glomerular epithelial cell marker of podocyte injury (podocytopathy) [80].

Although IgA isolated from patients with IgAN exerted no apoptotic effect on podocytes, in vitro studies revealed TNF- α released from glomerular mesangial cells after IgA deposition modulates the expression of Bcl-2 by podocyte through auto-amplification of TNF- α [81]. There is an apoptotic effect of mesangial derived-TNF- α on podocytes in chronic IgAN.

Mechanisms of Podocyte Injury in IgAN :

It is well demonstrated that a glomerulo-tubular cross-talk involving TNF- α exists in IgAN [51]. Lai *et al.* hypothesized that a similar glomerulo-podocytic cross-talk existed in IgAN [76]. Humoral factors/mediators from mesangial cells like TNF- α first activated the podocytes before reaching the tubulointerstitium either by glomerular filtration or by transportation via the post-glomerular capillaries. TNF- α receptor-1 (TNF-R1) and receptor-2 (TNF-R2) are constitutively present in normal podocytes. In vitro study suggests two functional roles played by the TNF-R1 in podocytes following stimulation by IgA-mesangial cell conditioned medium from patients with IgAN: IL-6 synthesis and apoptosis. Lai *et al.* suggests podocytes are in a chronic pro-inflammatory state in IgAN.

Clinicopathologic Findings :

Pathogenesis –

IgAN arises as a consequence of circulating IgA1-containing immune complexes binding to mesangial cells. The IgA1 in these complexes has a reduced content of galactose in hinge-region O-glycans to constitute a neoantigen that is recognized by circulating IgG or IgA1 [82]. The galactose deficiency accentuates binding of the IgA1 to mesangial cells. The resulting stimulation of mesangial cells leads not only to their proliferation as the light-microscopic hallmark of this renal disease, but also to synthesis of extracellular matrix and secretion of a host of cytokines/chemokines that may culminate in inflammation and scarring in the glomerular and tubulointerstitial compartments [83].

As a result of the glomerular damage, the filtration barrier is compromised and red blood cells and proteins enter the urinary space. These components may mediate additional injury, especially through interactions with podocytes and proximal tubular cells. Proximal tubular epithelial cells may also undergo transformation to mesenchymal cells and secrete extracellular matrix proteins to initiate interstitial scarring. Subsequent stimulation of fibroblasts/myofibroblasts in the renal interstitium augments the fibrosis [84].

Prognostic Factors :

Demographic Characteristics :

Among demographic features, male gender [85], and older age [14] and perhaps obesity[86] portend a worse long-term outcome for patients with IgAN.

Clinical Features :

Patients with at least one episode of synpharyngitic hematuria fared better than those who had never experienced this degree of glomerular bleeding [87]. There is nearly universal agreement that hypertensive patients fare less well than normotensive patients. The National Kidney Foundation in the United States recommends blood pressure <130/80 mm Hg for patients excreting < 200 mg protein per g creatinine per day and a lower target for patients excreting > 1000 mg protein per g creatinine per day.

Laboratory Findings :

Even mildly impaired eGFR (45–60 ml/min/1.73 m²) at the time of diagnostic biopsy have outcomes worse than those with normal clearance function.

Proteinuria has generally correlated with prognosis, although the threshold for a deleterious effect has been less clear. Analyses found a continuous-variable effect, with an adverse influence starting at 500 mg/day. More importantly, rather than one measurement at the time of biopsy, change in proteinuria over several years is a better gauge [88]. A study in Toronto showed that the cut-off was a time averaged value of 1 g/day, calculated as the average of six-month-interval means after diagnosis [89]. In one study, patients with microalbuminuria at biopsy were more likely to develop proteinuria,

hypertension, and renal insufficiency (eGFR < 60 ml/min/m²) 7.5 years later than were patients with normal albuminuria at biopsy [90].

Other laboratory features associated with worse outcome include hyperlipidemia and hyperuricemia.

Light-Microscopy Histology :

A low number of podocytes per glomerulus has been associated with worse proteinuria and a decrement in renal clearance function [91]. Other glomerular features signifying an unfavorable outcome include endothelial cellular proliferation, focal necrosis, focal segmental scars, extracapillary cellular proliferation (a crescent if involved area exceeds 10% of the circumference of Bowman's capsule) and global sclerosis.

Another vascular feature associated with poor prognosis is thrombotic microangiopathy [92].

Degree of interstitial damage is a better prognostic indicator than degree of injury within glomeruli [90]. Enumeration of fibroblasts after staining for fibroblastic-specific protein 1 (FSP1) has been correlated with extent of glomerulosclerosis and interstitial fibrosis. Other poor prognostic factors are intensity of staining for CD3+ lymphocytes, increased numbers of Mac387+ monocytes/macrophages and 27E10+ (activated) macrophages, intensity of interstitial staining for CD44, increased interstitial expression of iNOS, granule membrane protein of 17 kDa (GMP-17)-positive T-lymphocytes within renal tubules and B-lymphocytes in the interstitium.

Beyond Light Microscopy :

IgG in the mesangial immune deposits, immune deposits in the capillary loops on electron microscopy are other poor prognostic factors.

Potential New Prognostic Markers :

A high serum IgA/C3 ratio was correlated with worse histological lesions in non-nephrotic patients and a ratio above 4.5 indicated a worse renal survival [93].

Urinary IL-6 or the IL-6/epidermal growth factor ratio and greater amounts of IL-8, TGF- β , and transforming growth factor- α 1 have been proposed as markers of poor prognosis.

Genetic Markers :

Genes with polymorphisms associated with outcome include those encoding ACE-DD , angiotensinogen and CC-chemokine receptor in whites, and plasminogen activator inhibitor-1, selectin, Fc γ RIIa and Fc γ RIIIa, angiotensinogen, peroxisome proliferator - activated receptor γ , T-cell receptor, transforming growth factor- β 1, and paraoxonase.

Pathology based grading systems :

Classification Author/Year	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SPNSG/1982 ¹	Minimal glomerular changes	Mesangial proliferation only	Any focal or sclerotic lesion		
Haas/1997 ²	Minimal or no mesangial hypercellularity ; without sclerosis or crescents	Focal segmental glomerulosclerosis ;minimal increase in mesangial hypercellularity; no crescents	Focal proliferative changes , <50% glomeruli are hypercellular	Diffuse proliferative, > 50% glomeruli are hypercellular	Advanced sclerotic changes, ≥40% glomeruli are globally sclerotic and/or ≥40% tubular atrophy or loss of cortex
To/2000 ³	Mean glomerular sclerosis <25%. Tubular atrophy and interstitial fibrosis <5%	Mean glomerular sclerosis 25%-49%. Tubular atrophy and interstitial fibrosis 5%-49%	Mean glomerular sclerosis ≥50%. Tubular atrophy and interstitial fibrosis ≥50%.		
Lee/2005 ⁴	Normal or focal mesangial cellular proliferation	Diffuse mesangial cellular proliferation, or <25% of glomeruli with crescents, segmental/global sclerosis	25% to 49% of glomeruli with crescents, segmental/global sclerosis	50% to 75% of glomeruli with crescents, segmental/global sclerosis	>75% of glomeruli with crescents, segmental/global sclerosis
Wakai/2006 ⁵	Slight mesangial cell proliferation and increased matrix	Slight mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation or adhesion to Bowman's capsule in < 10% of glomeruli.	Moderate diffuse mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation or adhesion to Bowman's capsule in 10% to 30% of glomeruli	Severe diffuse mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation or adhesion to Bowman's capsule in > 30% of glomeruli	
Manno/2007 ⁶	Normal glomeruli or slight increase in mesangial matrix and/or cellularity	Moderate or diffuse mesangial proliferation and/or focal segmental sclerosis and/or endocapillary proliferative and/or cellular crescents in ≤50% of glomeruli	Cellular crescents in > 50% of glomeruli and/or global sclerosis and fibrous crescents involving > 1/3 of glomeruli and/or diffuse segmental sclerosis.		

SPNSG, Southwest Pediatric Nephrology Study Group

1. A multicenter study of IgA nephropathy in children. (1982) A report of the Southwest Pediatric Nephrology Study Group. *Kidney Int* 22: 643–652.
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5. Wakai K, Kawamura T, Endoh M, *et al.* (2006) A scoring system to predict renal outcome in IgA nephropathy: from a nationwide prospective study. *Nephrol Dial Transplant* 21: 2800–2808
6. Manno C, Strippoli GF, D'Altri C, *et al.* (2007) A novel simpler histological classification for renal survival in IgA nephropathy: a retrospective study. *Am J Kidney Dis* 49: 763–775.

Clinical Course of Primary IgA Nephropathy :

The definition of IgAN is still pathological and needs a renal biopsy for diagnosis. The agreed definition is the deposition of at least 1+ (on a semi-quantitative scale: 0 = no deposits; +/- = traces; 1+, 2+ and 3+) immunoglobulin A (IgA) in the mesangial area of glomeruli. The characteristics of these IgA deposits are the followings: granular, coarse with the “en mottes” aspect, predominantly mesangial, dominant or codominant with other immunoglobulins such as IgG and/or IgM, associated with C3 deposits at the same location, and global and diffuse in contrast to the light microscopy lesions which are often segmental and focal. Once the diagnosis of IgAN is made, the clinician has to differentiate the primary form, also called Berger's disease, which represents

about 80% of all cases from the secondary forms.

Comparisons between males and females showed that females had significantly less proteinuria, lower GOS, and lower serum IgA level . In general at time of diagnosis, the clinical presentation was less severe in females.

The natural history of primary IgAN is both clinical and pathological progression towards chronic renal failure (CRF) and end-stage renal failure (ESRF) [94 ,95]. In the literature, the cumulative incidence at 20 years of ESRF/dialysis varies from 10% to 40% depending on the policy of renal biopsy.

IgA Molecule in IgA Nephropathy :

Deposited IgA is predominantly polymeric IgA (pIgA) of the IgA1 subclass and has been shown to be differentially glycosylated. Moreover, vaccination studies have demonstrated alterations in mucosal immunity, whereas in many patients mucosal infections are associated with episodes of macroscopic hematuria.

Plasma IgA1 are elevated in about half of the IgAN patients [96]. The elevated IgA concentration seems to be the result of higher production of IgA by plasma cells in the bone marrow[97]. Next to the higher concentrations of IgA1, qualitative changes of IgA in IgAN patients have been described. IgA of IgAN patients contains a reduced galactosylation of the O-linked glycans in the hinge region [98].

Patients with IgAN have a hampered primary mucosal IgA immune response. As a result of this mucosal hyporesponse, the clearance of antigens might be less effective leading to a prolonged antigen exposition, which might eventually lead to higher levels of memory and higher IgA serum titers . The fact that other diseases with high serum

IgA concentrations, like multiple myeloma or HIV, are not associated with renal IgA depositions supports the idea that the higher IgA1 concentrations are not the only cause of mesangial IgA deposition in IgAN.

Dendritic cells (DC) might be less effective in inducing IgA production by naïve B cells. DC derived from IgAN patients showed a reduced capacity to induce IgA production in the presence of IL-10 [99]. However, so far it not clear which factors are responsible for the disturbed DC function in IgAN patients.

Galactose deficiency of IgA1 appears to be a key pathogenetic factor contributing to the development of the disease. Circulating complexes in IgA nephropathy contain IgA1 with galactose-deficient hinge-region O-linked glycans [82]. Notably, galactose-deficient IgA1 is the predominant glycosylation variant of IgA1 in the mesangium[100]. Cells from patients with IgA nephropathy had low expression and activity of the corresponding galactosyltransferase and high expression and activity of sialyltransferase. Consequently, the O-glycans on the secreted IgA1 are galactose deficient with high proportion of GalNAc being sialylated [101]. In view of the fact that sialylation was shown to prevent galactosylation of GalNAc, it is quite possible that “premature” sialylation helps to increase the levels of galactose-deficient O-glycans in IgAN.

After alteration of the glycosylation of the IgA1, neoepitopes represented by IgA1 glycans or hinge-region glycopeptides are exposed and recognized by naturally-occurring antibodies with anti-glycan or anti-glycopeptide specificities[102]. Clones of EBV transformed peripheral blood lymphocytes from IgAN patients in culture secrete IgG antibodies specific for galactose-deficient IgA1. Thus, the presence of glycan-specific anti-IgA1 antibodies promotes formation of immune complexes. The

resultant IgA1 complexes are relatively large. Because of their size, they are not efficiently cleared from the circulation and thus tend to deposit in the renal mesangium.

Galactose-deficient IgA1 is retained in the circulation for long periods of time. Galactose deficiency in itself should not hinder disposal of IgA1 molecules because the asialoglycoprotein receptor recognizes terminal GalNAc as well as galactose. However, if the GalNAc is linked to sialic acid or is covered by an antibody, it cannot be recognized by the hepatic asialoglycoprotein receptor and is not catabolized [103].

Immunopathogenesis of IgAN is considered to occur in three phases –

1. In the early **primary phase**, B cells produce polymeric IgA (pIgA) in response to variety of antigens that initiates glomerular IgA immune deposit formation.
2. In the **secondary phase**, continuous activation of the mesangial cells, the complement system and the innate immune system by persistent glomerular pIgA immune deposits attract macrophages that produce inflammatory mediators leading to glomerulosclerosis.
3. In the **tertiary phase**, interstitial infiltration by T cells cause tubular injury and sets in motion irreversible interstitial fibrosis leading to end stage renal failure in 20%–40% of the affected patients.

Antigen-Dependent Mechanism of IgA Nephropathy :

Since IgA is an important immunoglobulin in defense mechanisms against exogenous antigens in the mucosal system, the antigens might be located in the mucosal membranes of patients with IgA nephropathy. However, it is not still known whether

antigens are exogenous and/or endogenous in patients with IgA nephropathy. It is speculated that there are many kinds of antigens, i.e. food, virus, bacteria and/or fungus, in patients with IgA nephropathy as follows: (1) dietary antigens,(2) respiratory antigens, (3) intestinal antigens, (4) biliary antigens, and(5) dermal antigens. These antigens might form antigen-antibody dependent immune complexes.

Food components such as bovine albumin, ovalbumin , lactoglobulin , gliadin have been implicated.

IgA nephropathy is frequently preceded by episodes of upper respiratory tract infection that is presumed to have some viral etiology [104]. Virus-like particles and/or microtubular structures were occasionally observed in the glomerular mesangial areas by electron microscopy.

Slight deposition of *adenovirus*, *herpes simplex*, *varicella zoster* or *parainfluenza 3* virus was observed by immunofluorescence [106], the contributory role of which is debated.

IgA nephropathy has been described as a complication of infections with *Yersinia enterocolitica*, *Campylobacter jejuni*, and *Mycoplasma pneumoniae*. Suzuki *et al.* observed glomerular deposition of *Hemophilus parainfluenzae* antigens by immunofluorescence and the presence of IgA antibody against *H. parainfluenzae* in sera by enzyme-linked immunosorbent assay (ELISA) in patients with IgA nephropathy [16].

Complement Activation :

In addition to mesangial IgA deposits, biopsies of IgAN are commonly associated with the deposition of complement components, most notably C3, the membrane attack complex (C5b-9), and properdin, suggesting the participation of alternate pathway

complement in disease pathogenesis [108]. Local complement production by various intrinsic renal cells and infiltrating cells may contribute to tissue injury in IgAN [109].

Moreover, proteinuria but not serum creatinine, at the time of renal biopsy correlated with C3 mRNA expression. This last phenomenon may be attributed to the finding that apical proteins stimulated basolateral C3 synthesis by cultured human proximal tubular epithelial cells, in which transferrin and apotransferrin stimulated C3 biosynthesis more intensely. Locally secreted C3 may further activate tubular cells via the C3a receptor to enhance renal injury [110]. Evidence is accumulating that complement activation via MBL and the lectin pathway is also associated with disease progression in IgAN [111]. More recent data suggest that IgA was co-deposited with MBL in about 25% of patients and that MBL deposition showed more severe renal disease as compared with MBL-negative cases, suggesting an important role for MBL in disease progression [112].

Corticosteroids :

For decades, these agents have been used with the concept of a non-specific but very potent antiinflammatory effect.

In 1986 Kobayashi *et al.* first reported their experience coming from a prospective, non-randomized study of 14 IgAN patients with proteinuria between 1.0 and 2.0 g/day who received an initial dose of 40 mg/day of prednisolone, followed by gradual reduction of the dose over an average period of about 19 months. Compared to the 29 control subjects, patients treated with steroids had considerable reduction in proteinuria and better preserved renal function; those with creatinine clearance higher than 70 ml/min seemed to benefit more from therapy [113].

Encouraging results were also obtained in 13 children who were treated with alternate day prednisone 60 mg/m² for three months, reduced to 30 mg/m² by one year and 15 mg/m² by two years. In comparison with a historical group, Waldo *et al.* showed a significant improvement in urine analysis (both proteinuria and hematuria) and a preserved normal GFR. Follow-up biopsy after two years of treatment revealed a significant fall in the activity score (from 5.2 to 4.3), without any significant increase in the chronicity score [114].

Conversely, first reports coming from small, randomized clinical trials were mostly negative. Lai *et al.* found no benefit of prednisone (1 mg/kg/day for two months and a tapered dosage for another two months) in a controlled trial involving 34 patients with nephritic syndrome. However, the length of treatment (only four months) was perhaps not long enough [115].

Julian *et al.* made a multicenter prospective trial in IgAN patients with proteinuria greater than 2 g/day by comparing symptomatic therapy with alternate-day prednisone (60 mg/day tapered by 10 mg every three months to 10 mg/day over 24 months). However, they published only preliminary data of a small set of patients not supporting a favorable effect of steroids (only a modest reduction in proteinuria was observed) [116]. However, the lack of effectiveness on renal function may be due to a too short follow-up (nearly two years).

In 1987 Pozzi *et al.* started a large, multicenter, randomized, open-label, controlled trial in order to evaluate the effects of corticosteroids in 86 adult biopsy-proven IgAN patients with normal renal function (serum creatinine ≤ 1.5 mg/dl) and moderate proteinuria (1–3.5 g/day). The patients were randomly assigned to receive either supportive therapy or

six-months' steroid treatment (methylprednisolone 1 g intravenously for three consecutive days at the beginning of months 1, 3 and 5, plus oral prednisone 0.5 mg/kg every other day for six months). Baseline characteristics were comparable in the two groups. After five years of follow-up, renal survival was significantly better in the steroid treated patient group than in the control group for both the primary endpoints of 50% and 100% increase from baseline plasma creatinine levels (respectively of 17% and 21%; log-rank test $p < 0.048$ and $p < 0.005$). Evaluation of renal survival after ten years of follow-up confirmed that outcomes in the steroid-treated group were better than those in the control group (97% vs. 53%, $p = 0.0003$). Mean urinary protein excretion also significantly decreased in the steroid group (from 1.93 ± 0.45 g/day at baseline to 0.78 ± 0.41 g/day at one year), and this decrease persisted throughout the follow-up, whereas proteinuria remained unchanged in the control group. It is likely that treatment with ACE inhibitors or ARBs did not affect the findings, since a similar percentage of patients in both groups received these agents. Interestingly, glucocorticoids were effective in every histological class. This suggests that the main indication to steroid treatment in patients with IgAN should be proteinuria level and not indexes of activity and/or chronicity at renal biopsy examination. None of the patients in the steroid group experienced any major side effects [117].

More recently, in an open-label study, Katafuchi *et al.* randomized 90 IgAN patients with normal renal function to steroids (oral prednisolone 20 mg/day for one month followed by 15 mg/day for one month, 10mg/day for one month, 7.5 mg/day for three months and 5 mg/day for 18 months) plus dipyridamole (150 or 300 mg/day) or dipyridamole alone at the same dose. Steroids significantly reduced proteinuria, but

were ineffective on renal survival. However, the event rate was very low (only three patients in each group progressed to end-stage renal disease during follow-up) and the study was severely underpowered to show any effect on end-stage renal disease [118].

No controlled, randomized studies have yet been conducted comparing intravenous pulse with oral steroid for IgAN.

There are few studies evaluating the effect of glucocorticoids on histological lesions. Yoshikawa *et al.* studied 78 children with IgAN and normal renal function, 40 of whom received prednisolone, azathioprine, heparin/warfarin and dipyridamole for two years, and 38 heparin/warfarin and dipyridamole alone. Clinical and pathological data before treatment were similar in the two groups. In the second biopsy, performed after treatment, the mean percentage of glomeruli showing segmental or global sclerosis was unchanged in patients treated with glucocorticoid and azathioprine, but increased from 3.9% to 16.4% in patients who did not receive glucocorticoids [119].

There are few clinical studies testing steroid therapy in IgAN patients with advanced disease. Tamura *et al.* studied retrospectively 60 IgAN patients with creatinine clearance below 70 ml/min at the time of renal biopsy (on average 58 ml/min), 20 of whom received steroids. The mean follow-up period was about 4.5 years. After one year, proteinuria decreased in the steroid group (from 2.33 to 1.02 g/day), but remained unchanged in the non-steroid group (from 1.39 to 1.28 g/day). Interpretation of results is slightly biased by the fact that before treatment, proteinuria was higher in patients receiving steroids (2.33 vs. 1.39 g/day in the control group). Even if serum creatinine was unchanged after one year in the two groups, at the final observation patients not treated with steroids had higher creatinine values compared to those receiving steroids

(2.51 vs. 1.79 mg/dl, respectively) [120].

Renin-Angiotensin Blockade :

In recent years, two prospective RCTs [123,124] proved that in proteinuric IgAN with rather good glomerular filtration rate, a significant effect of ACEi not only in reducing proteinuria but also in preserving renal function, and another RCT[126] proved that ARB decreases proteinuria and slows renal deterioration after adjustment for blood pressure control. The additional benefit of a combination therapy has never been adequately addressed in IgAN by properly designed RCT, and only short-term studies or RCT sub-analysis are available, which suggest a possible superior effect of the combination therapy in reducing proteinuria and possibly renal disease progression.

Treatment of IgAN with ACEi :

A more recent prospective study pointed out a significant stabilization of GFR in IgAN only in the intensive treatment group, when BP was lowered to <130/70 mmHg (often using multidrug combinations), while patients with BP > 135/75 mmHg failed to be protected against functional decline [121].

Dillon in 2001 performed a meta-analysis of 237 IgAN patients treated with ACEi and enrolled in three short-term crossover trials, one prospective RCT and three retrospective studies, and concluded that the effect on proteinuria was clear, while the renoprotective effect remained unproved [122].

In 2003, a RCT of ACEi in IgAN was published by Praga *et al.* The trial was not placebo-controlled, and enrolled 44 subjects mainly of young age (< 40 years old) from

one single center with wide range of proteinuria (from 0.5 to 5 g/day) and various degrees of renal function impairment. Patients randomly assigned to enalapril or control group had similar baseline characteristics of GFR, proteinuria and BP. Enalapril was given at a starting dose of 5 mg/day and titrated to achieve and maintain a target BP of $\leq 140/90$ mmHg until a maximal dose of 40 mg/day. After a mean follow-up of 75 months, the proportion of patients developing the primary end point (50% increase of baseline plasma creatinine) was significantly lower in ACEi group than in the control group (12% versus 57%, respectively). After four years of follow-up, renal survival was 100% in treated patients versus 70% in controls and this trend worsened after eight years when the renal survival decreased to 55% in placebo, versus 92% in treated subjects. Proteinuria significantly decreased in the treated group from 2 ± 1.3 g/day (0.5–5.3) to 0.9 ± 1.3 g/day (0.5–5.3) ($p < 0.001$) while no significant changes were observed in the control group [123].

IgACE was the first placebo-controlled RCT designed to investigate the effects of ACEi in young IgAN patients (aged less than 35 years), with moderate proteinuria (> 1 and < 3.5 g/day/1.73 m²) and GFR > 50 ml/min/1.73 m². Sixty-six patients, meanly 20 years old (range 9–35), were randomized to receive benazepril 0.2 mg/kg/day or placebo, and were followed for a median of 38 months. The end point of progression of IgAN was defined as $> 30\%$ decrease of baseline creatinine clearance (CrCl) and also as a composite end point of $> 30\%$ decrease of baseline CrCl and/or worsening of proteinuria until ≥ 3.5 g/day/1.73 m² was considered. Secondary outcomes included proteinuria, partial (< 0.5 g/day/1.73 m²) or total remission (< 160 mg/day/1.73 m²) for more than six months. One single patient (3.1%) in the ACEi group and 14.7% in the placebo group

reached the end point of renal function decline. No patient on ACEi developed nephrotic syndrome, versus 20.6% on placebo group. The renal disease progression to the composite end point of renal function decline and worsening of proteinuria above the nephrotic range resulted significantly different between the two groups of ACEi treated patients and those assuming placebo($p = 0.035$). In conclusion, angiotensin antagonism was successful in limiting progression of renal damage in young IgAN patients with proteinuria between 1 and 3.5 g/day. ROC analysis identified 1 g/day/1.73 m² at one year as a cut-off level of proteinuria protective over progression. In the IgACE trial, patients with time average proteinuria < 1 g/day/1.73 m² had a favourable survival to 30% reduction of baseline CrCl (100% survival after 58 months of follow-up), while those with time-average proteinuria between 1 and 3 g/day/1.73 m² had 75% survival and those over 3 g/day/1.73 m² a 65% survival (log rank: $p = 0.01$) [124].

Treatment of IgAN with ARB :

In a short term study of 12 weeks, ARB therapy (losartan 50 mg) resulted superior to the calcium channel blocker treatment (amlodipine 5 mg) in reducing proteinuria and TGF- β 1 excretion, even though BP control was similar[125].

The long-term effects of ARB therapy in proteinuric IgAN have been recently demonstrated by Li *et al.* in a multicenter, placebo controlled RCT. They enrolled 109 patients from Hong Kong with IgAN and proteinuria greater than 1 g/day and serum creatinine level lower than 2.8 mg/dl, or serum creatinine level of 1.4 to 2.8 mg/dl, regardless of degree of proteinuria. Patients were assigned to valsartan, 80 mg/d

(titrated up to 160 mg/d for BP control), or placebo for 104 weeks. Additional antihypertensive therapy was allowed to achieve a target BP of 140/90 mmHg. Proteinuria decreased significantly in the treatment group but did not change in the placebo group. With multiple linear regression models, ARB treatment resulted in a 33% decrease in proteinuria after adjusting for other confounding factors. There was a significant decrease in mean rate of GFR decline in the ARB group (-5.62 ± 6.79 ml/min/year), compared with the placebo group (-6.98 ± 6.17 ml/min/year) throughout the study period after adjustment for average BP and proteinuria ($p = 0.014$). This RCT demonstrated that ARB significantly decreases proteinuria and slows renal deterioration in patients with IgAN after adjustment for confounding factors, notably BP [126].

Combination Therapy in Proteinuric IgAN :

In a short-term clinical investigation, doubling ACEi or ARB doses in 12 adults with IgAN did not improve the antiproteinuric effect. However, a higher effect was observed when the two drugs were co-administered and an additional reduction in proteinuria was obtained when combined therapy doses were doubled [127].

In 31 patients with IgAN and mild proteinuria (from 0.3 to 0.7 g/day), GFR > 50 ml/min and normal BP, the dual blockade of RAS given for six months was reported to induce remission of proteinuria in 63% of the cases versus 41% in ACEi and 36% in ARB monotherapies [128].

In conclusion, the additional benefit of a combination therapy has never been adequately addressed in IgAN by properly designed RCT; only short-term studies suggest a possible superior effect of the combination therapy in reducing proteinuria.

Cyclophosphamide in Combination with Corticosteroid :

In 2002, Ballardie *et al.* published a randomized, controlled, single center study on 38 patients with progressive loss of renal function. Patients, none of whom had crescentic glomerulonephritis, were randomized to prednisolone and low-dose cyclophosphamide followed by azathioprine or supportive therapy only. Renal survival in treated patients showed considerably better preservation of function at five years (72% compared with 6% in controls). Proteinuria and erythrocyturia reduced from 12 and six months of treatment, respectively. No side effect was reported apart from marrow suppression in one subject and pulmonary tuberculosis in another. This study may be faulted, however for suboptimal blood pressure control and insufficient use of medications that block the angiotensin system, the unusually poor survival rate of the placebo group, and the small number of patients [129].

Tumlin *et al.* conducted a prospective, uncontrolled, open-label trial of 12 patients with crescentic IgAN and clinically progressive disease. Treatment consisted of three doses of methylprednisolone at 15 mg/kg/day, followed by intravenous cyclophosphamide at 0.5 g/m² /month for six months. Serum creatinine fell from 2.7 to 1.5 mg/dl, and proteinuria decreased from 4 to 1.3 g/day after treatment, suggesting a beneficial role of cyclophosphamide in crescentic glomerulonephritis [130].

Mitsuiki *et al.* retrospectively examined the outcome of 35 patients with histologically advanced IgAN, in whom 27 received prednisolone for two years and oral cyclophosphamide (50mg/day) for six months, and the remaining eight received

supportive treatment. Renal prognosis was significantly better in the treatment group [131].

Overall, these studies suggest that combined cyclophosphamide/steroid therapy may benefit IgAN patients at very high risk of renal failure, namely those with a progressive decline in GFR and/or crescentic lesions before randomization. However, more definitive evidence involving patients in sufficient numbers is required before this treatment can be widely accepted.

Cyclosporin :

Lai *et al.* conducted a randomized prospective single blind study of 19 patients with proteinuria > 1.5 g/day. Patients who received cyclosporin had significant reduction of proteinuria, serum IgA, and increase of plasma albumin concentration compared with placebo. However, there was transient deterioration of renal function during treatment, despite within-range trough drug levels. The authors discouraged indiscriminate use of cyclosporin in IgAN due to nephrotoxicity [132].

Azathioprine :

Goumenos *et al.* performed a retrospective analysis of 74 IgAN patients followed for ten years, and found that long-term azathioprine combined with low-dose prednisone did not alter the clinical course compared to untreated controls. However, in a subgroup of patients with heavy proteinuria greater than 3 g/day and baseline serum creatinine

between 1.4–2.5mg/dl, this immunosuppressive regimen reduced the risk of doubling serum creatinine compared to controls (27% vs. 78%) and delayed progression to end-stage renal failure (17% vs. 55%) [133].

The Japanese Pediatric IgA Nephropathy Treatment Study Group randomized 78 children with newly diagnosed early IgAN to receive either prednisolone, azathioprine, heparin-warfarin, and dipyridamole or the combination of heparin-warfarin, and dipyridamole only. After two years, there was significant reduction of proteinuria and serum IgA levels in the prednisolone/azathioprine group, while there was no difference in renal function between the two groups. The study was flawed by a lack of data on baseline proteinuria and creatinine clearance as well as blood pressure control in both groups [134].

Mycophenolate Mofetil :

To date, four randomized clinical trials have been published on the use of MMF in IgAN, which add more controversy than consensus.

The first randomized study, published in 2002 in the Chinese literature, was conducted in Beijing in which 62 Chinese patients with severe IgAN with Lee's grade IV and V renal histology and urinary protein > 2.0 g/d received MMF or oral prednisone for at least 12 months. After 18 months' follow up, the MMF group showed significant improvement in proteinuria and serum lipids than the prednisone group [135].

In 2004 Maes *et al.* described a prospective study in 34 Belgian patients with impaired renal function who were randomized to 2 g of MMF (n = 21) or placebo (n =

13) after instituting salt restriction and angiotensin-converting enzyme inhibitor therapy in all. They only included patients with histologic unfavorable criteria and arterial hypertension, and excluded those with mild histopathologic changes despite heavy proteinuria. After three years of follow-up evaluation, inulin clearances and proteinuria did not differ between the groups [136].

In 2005 Tang *et al* published a prospective study in 40 Chinese patients with IgAN and mild tubulointerstitial lesions who were randomized 1:1 to 1.5 (BW < 60 kg) or 2.0 g/day MMF for six months or continuation of contemporaneous medication only after blockade of the renin-angiotensin system failed to reduce proteinuria to < 1 g/d. Twelve months after stopping MMF, the overall remission rate (proteinuria < 0.3 g/d or 50% of baseline) was significantly higher in MMF-treated patients whose proteinuria dropped to 62% of baseline, whereas urine protein in control patients increased to 120% of baseline. Adverse events in the MMF group included anemia, urinary tract infections and cervical lymphadenitis. There were no adverse events in the control group [137].

In late 2005, Frisch *et al.* published a randomized controlled trial in which 32 predominantly Caucasoid North American patients with advanced IgAN (mean serum creatinine, 2.5mg/dl) were randomized to MMF or placebo. MMF was given for one year as a “salvage” therapy in 16 patients with advanced renal insufficiency. Notably, the presence of glomerulosclerosis or tubulointerstitial atrophy and fibrosis on renal biopsy was an inclusion criterion. The study was terminated prematurely after observing a trend towards worse outcome in the MMF group [138].

Overall, MMF appears to be effective in reducing proteinuria in Chinese but not Caucasoid IgAN subjects. Therefore, ethnic differences may be one possible reason to

account for the differences observed in these studies. Another possibility is the mild histologic grade in Tang's study versus the moderate-to-severe grades in the studies by Maes and Frisch. Further observation and studies are needed to provide more definitive answers on the efficacy of MMF in IgAN.

Other Immunomodulatory Therapy :

Lai *et al.* had performed plasma exchanges for two patients with crescentic IgA in whom corticosteroid and immunosuppressive therapy failed to control the progression of the disease. In both cases, the rapid progression of renal failure was apparently halted. Nevertheless, the long-term benefit of plasma exchange in crescentic IgA nephropathy was unsatisfactory as the renal function continued to deteriorate in the following 12 months despite an initial stabilization [139].

Lou *et al.* showed in 60 patients randomized to leflunomide or fosinopril that leflunomide effectively suppressed proteinuria, however this effect was not superior to that achieved by fosinopril [140].

In a study that employed 41 historical pediatric controls who received prednisolone, warfarin, and dipyridamole therapy before 1989, the addition of mizoribine in 20 subjects after 1990 appeared to be more effective in ameliorating proteinuria and histological severity on repeat biopsy at two years [141].

Intravenous immunoglobulins, given monthly at a dose of 2 g/kg body weight for six months to eight patients with progressive IgAN, showed some benefit in prolonging renal survival by 3.5 years compared with eight patients with IgAN and similar level of renal function without receiving immunoglobulins [142].

Information of Rituximab (anti-CD20 antibody) for treatment of IgAN is lacking.

Fish Oil :

The rationale for using fish oil supplements in patients with IgAN is based on experimental data suggesting that omega-3 polyunsaturated fatty acids may limit the immunologic renal injury in IgAN. These omega-3 fatty acids compete with arachidonic acid to produce trienoic eicosanoids which, in turn, may slow renal disease progression by reducing glomerular and interstitial inflammation, mesangial cell contractility, platelet aggregation, and vasoconstriction in response to renal injury [143].

There have been six RCTs of fish oil (EPA and DHA) in IgAN. Two trials by the Mayo Nephrology Collaborative Group have demonstrated a renoprotective effect of fish oil in patients with persistent proteinuria[144,145].

The first of these was an RCT of 106 patients with proteinuria > 1 g/24 hours and impaired renal function at enrolment (60% also hypertensive) which found that those treated with fish oil had a slower rate of decline in GFR (but no improvement in proteinuria) at both two and five years[144].

A second RCT from the same center, included a further 73 patients with similar baseline characteristics, but used a historical control group (the authors argued it was inappropriate to include a control group in light of the benefits of fish oil in the initial study). Again, fish oil was associated with a slower rate of decline in GFR compared to the historical control group and this effect was independent of the dose of fish oil used [145].

These results have not been replicated in three other RCTs studying similar patient cohorts [146, 147, 148] and a meta-analysis (three trials, 175 patients) failed to detect a benefit of fish oils on renal outcome in IgAN [149].

At present the available evidence does not yet give unequivocal support for the use of fish oil and a further confirmatory study of fish oil in IgAN would be of great value. There is no data in published clinical trials suggesting a synergistic or otherwise effect of co-administration of ACEI/ARB and fish oil.

Tonsillectomy :

There are many experimental studies suggesting the involvement of a tonsillar autoimmune response in the pathogenesis of IgAN. Tonsillectomy is commonly performed in Japan for IgAN, especially combined with steroid pulse therapy, whereas it is only rarely performed in European countries and the USA. The main reason for this deep controversy is the lack of evidence from randomized controlled trials (RCTs).

Japanese studies show that tonsillectomy is beneficial only if done at an early stage of disease .The Okayama group in Japan followed 85 IgAN patients, 43 of whom had undergone tonsillectomy. They originally reported unfavorable results on renal survival at five years after the tonsillectomy. However, they subsequently recognized the favorable effects of tonsillectomy on renal survival rates after an observation period of ten years. The renal survival rate at ten years was 95.1% in the tonsillectomy group and 73.3% in the non-tonsillectomy group [150].

Similarly, the Niigata group followed 118 patients with IgAN in which 48 underwent tonsillectomy, for 192.9 ± 74.8 months, and reported a favorable renal survival rate, as assessed by Kaplan-Meier analysis, in the tonsillectomy group [151].

Effect of Tonsillectomy plus Steroid Pulse Therapy :

Tonsillectomy and steroid pulse therapy have been demonstrated to be independent contributing factors for clinical remission. The likelihood of clinical remission (i.e. disappearance of both hematuria and proteinuria) with tonsillectomy per se is less than 50% even in patients with early-stage IgAN. On the other hand, a marked increase in the likelihood of clinical remission may be expected when tonsillectomy is combined with steroid pulse therapy in patients with early stage IgAN, which is approximately 80% of patients treated [152].

While clinical remission is highly unlikely, slowing of disease progression by tonsillectomy plus steroid pulse therapy may be expected even in patients with advanced IgAN, if the serum creatinine level is under 2.0 mg/dl [153].

Unfortunately, there are no RCTs comparing steroid pulse therapy combined with tonsillectomy versus steroid pulse therapy alone. A multicenter prospective cohort study from Japan indicates a higher likelihood of clinical remission with steroid pulse therapy combined with tonsillectomy than with steroid pulse therapy alone, even in moderately advanced IgAN patients[154].

Indications of Tonsillectomy in Patients with IgAN :

The principle for tonsillectomy in IgAN patients is “the earlier the better.” The indications for tonsillectomy in patients with IgAN remain controversial. Some nephrologists contend that tonsillectomy should be restricted to IgAN patients suffering from recurrent episodes of tonsillitis or showing macroscopic hematuria after an episode of pharyngitis. Matsutani *et al.*, however demonstrated that the remission rates of both proteinuria and hematuria following tonsillectomy plus steroid pulse therapy were similar regardless of the history of recurrent tonsillitis, history of synpharyngitic gross hematuria, presence of pus plugs in the tonsillar lacunae, size of the tonsils, age or the results of the tonsillar provocation test [155]. Advancing histological score or clinical stage decreases the likelihood of clinical remission by tonsillectomy, regardless of whether or not it is combined with steroid therapy.

Therefore, the indications for tonsillectomy should be tentatively determined based mainly on the clinical or histological stage, with less importance attached to other parameters such as episodes of synpharyngitic gross hematuria, gross appearance of the tonsils or results of the tonsillar provocation test.

Future Prospects for IgA Nephropathy :

Diagnosis of IgA Nephropathy :

Presently, a renal biopsy is required for the accurate diagnosis of IgA nephropathy. It seems likely that in the not too distant future, a non-invasive diagnosis of IgA nephropathy will be possible. This will likely come from an extension of current studies

showing increased levels of under-galactosylated IgA1 in the circulation [156]. Urinary proteomics also shows great promise for non-invasive diagnosis of IgAN [157].

However, even if an accurate and reliable means of non-invasively diagnosing IgA nephropathy emerges, renal biopsy will remain as an important tool for rational decision making with regards to treatment and perhaps also for prognosis.

Prognostication in IgA Nephropathy :

Use of new tissue markers of prognosis, such as those which can be obtained by special immunohistochemical studies for examining deposition of specific proteins (such as fibroblast specific protein-1), in-situ hybridization studies for cytokine expression, microdissection for mRNA and RNAi expression and studies of infiltration of renal tissue with immune cells carrying specific markers (such as GMP-17+ T cells) may overtake the conventional approach. This new wave of “modern” renal pathology will likely replace the older approaches to morphology and will offer new avenues for more accurate prognostication based on tissue biopsy, even in “early” disease before progression to renal insufficiency has occurred [158]. Urinary markers of progressive disease are also likely to be increasingly described and validated [159].

Treatment of IgA Nephropathy :

While real progress has no doubt been made, in terms of reducing the rate of progression of disease, no therapy for IgA nephropathy is truly “curative.” Eventually

palliative therapy must give way to more effective modification of the fundamental disease processes, based on specific molecular or cellular events (so-called “designer” drug therapy). It is also very probable that pharmaco-genomics will make significant modification to the therapeutic approaches to IgA nephropathy in the not too distant future.

Aims

AIM :

To assess the efficacy of mycophenolic acid (MPA) in improving renal function and reducing proteinuria in high risk primary IgA nephropathy (IgAN) patients.

Abbreviations used :

IgA N – Immunoglobulin A Nephropathy

MPA – Mycophenolic acid

MAP – Mean arterial pressure

ACE-I – Angiotensin converting enzyme inhibitor

ARB – Angiotensin receptor blocker

e GFR – Estimated glomerular filtration rate

Abb. MDRD – Abbreviated modification of diet in renal disease formula

TDM – Therapeutic drug monitoring

Patients and methods

PATIENTS AND METHODS :

Inclusion criteria :

Patients with biopsy confirmed IgA Nephropathy (based on presence of predominant mesangial IgA deposits) and who have **any one** of the following features were deemed to be at high risk of progression –

1. Mean arterial pressure ≥ 107 mm Hg
2. eGFR at presentation < 60 ml/min/1.73 m² (Abb. MDRD)
3. Proteinuria > 3 gm/day
4. Glomerulosclerosis $\geq 50\%$ on renal biopsy

Exclusion criteria :

1. Age < 12 years
2. Secondary causes of IgA Nephropathy like liver diseases etc.
3. Henoch Schonlein nephritis

This is both a prospective and retrospective study wherein biopsy proven IgA Nephropathy patients who were diagnosed at CMC Hospital were identified from our renal biopsy records (2003 to 2009) and those at high risk of progression were identified based on the above criteria (from OPD charts and investigations from our computer database in case of retrospective patients) . Patients who were biopsied before 2008 were

identified from records whereas those enrolled from 2008-09 were prospectively followed.

Such patients who were treated with mycophenolic acid with steroids and antihypertensives and who had atleast 3 months of followup (MPA group) were compared with historical controls taken from an earlier published study from our institution [160]. Dose of mycophenolic acid was started at 30 mg per kg body weight and subsequently adjusted according to therapeutic drug monitoring(TDM) (6 hour area under curve) which is done in our Clinical pharmacology department. Regarding MPA, it is questionable whether standard dose therapy is the best way to treat a patient, given the large inter-individual variability in pharmacokinetics[162]. Several studies have shown a correlation between MPA exposure and efficacy[163]. Neumann *et al.* reported on the value of measuring MPA plasma concentrations in patients with autoimmune diseases[164]. The same may hold true in IgAN although it was not studied. Hence, we used TDM in determining MPA dose.

Steroids were started at 1mg per kg body weight on alternate days and continued for 3 months following which they were tapered gradually by 10 mg reductions on alternate days until they were stopped. Doses of antihypertensives including angiotensin converting enzyme inhibitors/angiotensin receptor blockers wherever possible were adjusted according to the target blood pressures which is <130/80 mm Hg .

2 groups of controls were taken, first being that treated with steroids and antihypertensives (steroid group), second group being that treated with antihypertensives only (no steroid group) i. e. without any immunosuppression. All the details including

history, clinical examination and laboratory parameters were recorded as per the proforma.

All patients were analysed at the end of 3 months follow up with regard to proteinuria and renal function expressed in terms of serum creatinine and eGFR (estimated glomerular filtration rate by Abbreviated MDRD formula). Only patients who could complete treatment without any interruptions due to non compliance or side effects requiring dose reduction were taken for analysis .

Continuous data was presented as mean \pm SD unless otherwise specified. Comparison of continuous variables was done by the t test or Mann whitney U test where appropriate. SPSS software 15 was used for statistical analysis. p value < 0.05 was considered as significant .

Proforma

PROFORMA

Name : Hosp. No. :

Age : Sex : M / F Ph. No. :

Presentation :

Preceding infection : Y / N Sore throat : Y / N

G.I .Infection : Y / N Other infection :

Nephrotic syndrome : Y / N

Acute nephritis : Y / N

Nephritic-nephrotic :

Recurrent macrohematuria : Y / N

Uremic symptoms/Renal failure : Y / N

Rapidly progressive renal failure : Y / N

Systemic hypertension : Y / N

Malignant hypertension : Y / N

Incidentally diagnosed : Y / N

Duration of symptoms :

Clinical features :

Blood pressure : Mean arterial pressure :

Pedal edema : Y / N Ht(cm) : Wt(kg) : BMI :

C.V.S. :

R.S :

P/A :

C.N.S :

Follow up : Y / N

Duration of follow up :

Investigations :

	At pres.	3 mon.	6 mon.	Last f/u
Urine RBC's				
24 hr up or up/uc				
B. Urea				
S. Creat.				
S. Uric acid				
S. Chol.				
S. Trigly.				

	At pres.	3 mon	6 mon.	Last f/u.
S.Total prot.(g/dl/)				
S.Alb(g/dl)				
GFR(ml/min/1.73m2)				
% Diff. in GFR				

Date of biopsy :

Biopsy No. :

Hass staging of pathology :

Global sclerosis : Absent / <50% / >50%

Mesangial involvement : Absent / Mild / Moderate - Severe

Interstitial involvement : Absent / Mild / Moderate - Severe

Interstitial fibrosis : Absent / Mild / Moderate - Severe

Vascular involvement : Absent / Mild / Moderate - Severe

Tubular atrophy : Absent / Mild / Moderate – Severe

Ig A Deposits :

Ig G Deposits :

Ig M Deposits :

C 3 Deposits :

Degree of crescents : Absent / Mild / Moderate – Severe

Drug therapy : MMF / MMS + one of the following -

1. Fish oil + ACE -I
2. CRF Management
3. Steroid + Fish oil + ACE –I
4. Fish oil + Anti HTN
5. Steroid

6 HR. MPA AUC :

At pres.	3 mon.	6 mon.	Last f/u

Side effects of MMF :

Diarrhea : Y / N

Leukopenia : Y / N

Infection : Y / N

Focus of infection :

Other side effects :

Status after treatment :

0 - No follow up

1 - Presenting with GFR <85 and >20 % progression

2 - Presenting with GFR <85 and <20 % progression

3 - Presenting with GFR >85 and >20 % progression

4 - Presenting with GFR >85 and <20 % progression

Renal survival : 1 - Yes

2 - No at presentation

3 - No at follow up

GFR decrease in ml/min :

Mode of RRT : 0 - No RRT

1 - HD

2 – CAPD

3 - Transplant

Master chart

Description of terms used in master chart :

Hosp No . – Hospital number given to a patient at the time of registration

Age – Age of the patient

Sex – 1 – male

2 – female

Meanartp – Mean arterial pressure

Up24hrs – 24 hour urine protein at baseline

Screat – Serum creatinine at baseline

Gfr – Estimated glomerular filtration rate at baseline

Up24h3 – 24 hour urine protein at 3 months followup

Screa3 - Serum creatinine at 3 months followup

Gfr3 - Estimated glomerular filtration rate at 3 months followup

Globscle – 0 – Absent

1 – Mild (<50%)

2 – Moderate (>50%)

Group – 1 – Case

2 – Control 1

3 – Control 2

Up_abd – Absolute difference in 24 hour urine protein between 3 months followup and at baseline

Up_ppd - Difference in percentage in 24 hour urine protein between 3 months followup and at baseline

Sc_apd - Absolute difference in serum creatinine between 3 months followup and at baseline

Sc_ppd - Difference in percentage in serum creatinine between 3 months followup and at baseline

Gfr_abd - Absolute difference in e GFR between 3 months followup and at baseline

Gfr_ppd - Difference in percentage in e GFR between 3 months followup and at baseline

Sno	Age	Sex	meanartp	up24hrs	screat	gfr	up24h3	screa3	gfr3	globscle	group	up_apd	up_ppd	sc_apd	sc_ppd	gfr_apd	gfr_ppd
1	33	1	97	0.6	1.9	37.4	2.1	1.5	57.29	2	1	1.51	255.93	-0.4	-21.05	19.89	53.18
2	43	1	120	2	2.6	28.8	1.1	2.1	36.8	2	1	-0.9	-45	-0.5	-19.23	8	27.78
3	43	2	97	3.8	2	29	1.9	1.7	34.86	1	1	-1.9	-50	-0.3	-15	5.86	20.21
4	50	2	109	1.3	2.5	21.6	0.62	1.4	42.3	0	1	-0.68	-52.31	-1.1	-44	20.7	95.83
5	22	1	107	1.2	1.7	53.8	0.39	1.7	53.8	2	1	-0.81	-67.5	0	0	0	0
6	38	1	140	3.3	2	39.9	0.36	1.6	51.7	2	1	-2.94	-89.09	-0.4	-20	11.8	29.57
7	36	1	97	1.2	2.8	27.3	0.11	2.3	34.3	2	1	-1.09	-90.83	-0.5	-17.86	7	25.64
8	44	1	99	2.2	1.9	41.1	4.8	1.5	54	2	1	2.6	118.18	-0.4	-21.05	12.9	31.39
9	25	1	87	1.2	1.8	49.1	0.5	1.5	60.6	2	1	-0.7	-58.33	-0.3	-16.67	11.5	23.42
10	28	1	97	5.3	5.6	13.15	3.44	3.8	20.5	2	1	-1.86	-35.09	-1.8	-32.14	7.35	55.89
11	24	2	120	3.2	2.2	29.15	0.38	2.3	27.7	2	1	-2.82	-88.13	0.1	4.55	-1.45	-4.97
12	21	1	110	4	2.6	33.28	.	2.6	33.28	2	1	.	.	0	0	0	0
13	32	1	93	3.1	3.9	19.14	1.3	2.6	30.5	2	1	-1.8	-58.06	-1.3	-33.33	11.36	59.35
14	39	1	97	2.3	1.6	51.4	0.93	1.9	42.15	.	1	-1.37	-59.57	0.3	18.75	-9.25	-18
15	37	1	113	0.4	2.9	26.16	0.45	2.3	34.2	.	1	0.05	12.5	-0.6	-20.69	8.04	30.73
16	32	1	.	0.1	2	41.36	0.09	1.6	53.5	.	1	-0.01	-10	-0.4	-20	12.14	29.35
17	33	1	107	1.3	4.8	15	0.3	3.5	21.5	2	1	-1	-76.92	-1.3	-27.08	6.5	43.33
18	45	2	.	2.4	2	28.64	1.7	1.7	34.54	2	1	-0.7	-29.17	-0.3	-15	5.9	20.6
19	21	2	97	0.6	1.7	40.32	0.08	2	33.43	1	1	-0.52	-86.67	0.3	17.65	-6.89	-17.09
20	37	1	110	4.4	2	40.16	0.02	1.5	55.9	1	1	-4.38	-99.55	-0.5	-25	15.74	39.19
21	34	2	110	4.2	2.1	28.65	0.56	2.4	24.5	2	1	-3.64	-86.67	0.3	14.29	-4.15	-14.49
22	41	1	.	1.8	2.5	30.4	0.74	1.8	44.4	0	1	-1.06	-58.89	-0.7	-28	14	46.05
23	33	1	133	2.3	3.2	23.9	0.96	3	25.7	1	1	-1.31	-57.71	-0.2	-6.25	1.8	7.53
24	24	2	117	2.5	3	20.4	.	2.9	21.2	2	1	.	.	-0.1	-3.33	0.8	3.92
25	34	1	93	2.7	1.6	52.8	1.6	1.5	56.9	2	1	-1.1	-40.74	-0.1	-6.25	4.1	7.77
26	35	1	130	7.3	6.8	38.4	1.2	1.8	45.9	.	1	-6.1	-83.56	-5	-73.53	7.5	19.53
27	30	1	93	6	2.4	34	2.7	1.9	44.5	1	1	-3.3	-55	-0.5	-20.83	10.5	30.88
28	41	1	.	2.1	1.6	50.8	0.06	1.4	59.4	2	1	-2.04	-97.14	-0.2	-12.5	8.6	16.93
29	38	1	107	1	1.5	55.7	1.4	1.4	60.3	1	1	0.44	45.83	-0.1	-6.67	4.6	8.26
30	38	1	107	1.9	2.8	27	0.78	2.1	38	2	1	-1.12	-58.95	-0.7	-25	11	40.74
31	30	1	107	9.7	2.4	34	4	2.3	35.7	1	1	-5.7	-58.76	-0.1	-4.17	1.7	5
32	48	1	103	1.9	2.2	34	1	2	38	1	1	-0.9	-47.37	-0.2	-9.09	4	11.76
33	35	1	93	5.9	1	90.4	0.9	1	90.4	0	1	-5	-84.75	0	0	0	0
34	30	1	110	8.1	3.1	25.3	5.8	2	42	2	1	-2.3	-28.4	-1.1	-35.48	16.7	66.01
35	30	2	137	1.8	1.1	62	0.5	1.1	62	1	1	-1.3	-72.22	0	0	0	0
36	38	1	143	3.8	2.4	32.4	3.4	2.4	32.4	2	1	-0.4	-10.53	0	0	0	0
37	22	1	93	2.3	2	44.6	0.2	2.4	36	1	1	-2.1	-91.3	0.4	20	-8.6	-19.28
38	41	1	94	1.7	2.8	26.7	1.57	1.9	41.7	2	1	-0.13	-7.65	-0.9	-32.14	15	56.18
39	34	1	97	2.3	3.3	23	0.6	3	26	2	1	-1.7	-73.91	-0.3	-9.09	3	13.04
40	29	2	117	3.3	2.5	24.2	0.97	2.4	25.4	.	1	-2.33	-70.61	-0.1	-4	1.2	4.96
41	47	1	97	0.7	1.8	43.2	0.3	1.8	43.2	1	1	-0.4	-57.14	0	0	0	0
42	33	2	97	3.1	3	19.19	2	2.6	59.4	1	2	-1.1	-35.48	-0.4	-13.33	40.21	209.54
43	40	2	83	1.7	1.2	54.25	0.528	1.2	52.88	1	2	-1.17	-68.94	0	0	-1.37	-2.53
44	37	2	93	1.6	1.1	59.3	1.1	1.1	59.4	1	2	-0.5	-31.25	0	0	0.1	0.17
45	38	1	97	1.5	3.5	20.9	0.82	1.9	42.38	0	2	-0.68	-45.33	-1.6	-45.71	21.48	102.78
46	64	1	97	4.7	1.7	45.13	.	5	12.48	2	2	.	.	3.3	194.12	-32.65	-72.35
47	50	1	100	7.9	1.9	40.02	5.6	1.9	40.08	1	2	-2.3	-29.11	0	0	0.06	0.15
48	27	1	140	1.8	1.1	85.2	0.07	1	95.27	1	2	-1.73	-96.11	-0.1	-9.09	10.07	11.82
49	16	1	100	5.5	0.6	188.4	0.18	0.7	159.89	1	2	-5.32	-96.73	0.1	16.67	-28.51	-15.13

50	14	1	91	3.6	0.8	135.2	0.49	0.5	242.24	0	2	-3.11	-86.39	-0.3	-37.5	107.04	79.17
51	21	2	103	1.8	3.8	15.3	6.2	5.7	12.08	2	2	4.4	244.44	1.9	50	-3.22	-21.05
52	42	2	117	2.4	3.3	16.27	1.8	4.3	12.01	2	2	-0.6	-25	1	30.3	-4.26	-26.18
53	24	1	113	7.7	2.4	35.47	2.9	2	43.85	1	2	-4.8	-62.34	-0.4	-16.67	8.38	23.63
54	32	1	111	0.9	1.1	82.32	0.8	1	92.04	1	2	-0.1	-11.31	-0.1	-9.09	9.72	11.81
55	33	1	133	20.7	4.6	15.69	2.1	1.2	74.11	1	2	-18.6	-89.86	-3.4	-73.91	58.42	372.34
56	42	1	117	1.3	3.6	19.83	0.88	2.1	37	1	2	-0.42	-32.31	-1.5	-41.67	17.17	86.59
57	65	1	107	7.7	0.9	89.86	1.4	0.9	90.01	0	2	-6.3	-81.82	0	0	0.15	0.17
58	26	1	110	4.3	1.1	85.86	3.2	1.2	77.79	1	2	-1.1	-25.58	0.1	9.09	-8.07	-9.4
59	16	1	103	3.6	1.6	61.49	3.1	1	105.94	0	2	-0.5	-13.89	-0.6	-37.5	44.45	72.29
60	45	2	104	4.2	1.2	69.47	3.1	1.2	51.63	1	2	-1.1	-26.19	0	0	-17.84	-25.68
61	27	2	93	0.4	4.4	12.77	0.06	3.6	24.28	1	2	-0.37	-85.95	-0.8	-18.18	11.51	90.13
62	35	2	97	4.7	1.7	45.13	0.29	1.2	54.34	2	2	-4.41	-93.83	-0.5	-29.41	9.21	20.41
63	46	1	111	3.5	1.1	76.47	0.94	1	85.5	0	2	-2.56	-73.14	-0.1	-9.09	9.03	11.81
64	26	1	114	3.6	2.3	36.65	0.11	1.9	45.77	2	2	-3.49	-96.94	-0.4	-17.39	9.12	24.88
65	20	1	97	12.8	1.6	58.7	2.4	1.4	68.67	1	2	-10.4	-81.25	-0.2	-12.5	9.97	16.98
66	18	1	96	8.2	1.5	64.68	6.8	2.1	43.94	1	2	-1.4	-17.07	0.6	40	-20.74	-32.07
67	35	2	98	5.9	1.1	59.98	6.9	1.1	60	1	2	1	16.95	0	0	0.02	0.03
68	35	1	86	3	1.7	48.91	2.9	1.3	66.77	1	2	-0.1	-3.33	-0.4	-23.53	17.86	36.52
69	45	2	95	0.2	4.8	10.41	3.4	2.5	28.64	0	2	3.16	1340.68	-2.3	-47.92	18.23	175.12
70	19	2	114	6.4	0.8	98.05	3.5	1	68.7	2	2	-2.9	-45.31	0.2	25	-29.35	-29.93
71	60	2	116	0.8	1.5	37.59	.	2	30.9	2	2	.	.	0.5	33.33	-6.69	-17.8
72	31	1	118	18	2.1	39.28	0.18	1.1	83	0	2	-17.82	-99	-1	-47.62	43.72	111.3
73	25	1	109	0.7	2.8	29.44	2.5	5	15.1	1	3	1.84	277.64	2.2	78.57	-14.34	-48.71
74	76	1	113	0.4	1.5	48.28	0.39	1.9	36.82	1	3	-0.06	-12.36	0.4	26.67	-11.46	-23.74
75	25	1	107	2.7	4	19.51	0.5	1.6	56.26	0	3	-2.2	-81.48	-2.4	-60	36.75	188.36
76	30	2	107	4.3	4.5	12.18	0.38	5.4	9.88	2	3	-3.92	-91.16	0.9	20	-2.3	-18.88
77	22	1	111	2.6	2.1	20.7	6.4	2.5	34.5	2	3	3.8	146.15	0.4	19.05	13.8	66.67
78	31	1	107	4.4	2.3	19.6	2.5	2	41.63	1	3	-1.9	-43.18	-0.3	-13.04	22.03	112.4
79	44	1	96	1.6	1.6	50.67	0.764	1.5	54.04	1	3	-0.84	-52.25	-0.1	-6.25	3.37	6.65
80	25	1	110	1.6	1.6	56.18	1.2	1.8	49.11	1	3	-0.4	-25	0.2	12.5	-7.07	-12.58
81	33	2	113	4.4	2.7	21.54	4.1	4.2	12.95	1	3	-0.3	-6.82	1.5	55.56	-8.59	-39.88
82	40	1	97	1.2	1.6	51.05	0.625	1.5	55.09	0	3	-0.58	-47.92	-0.1	-6.25	4.04	7.91
83	28	1	123	2.6	2.7	30.01	2.9	3.9	19.66	1	3	0.3	11.54	1.2	44.44	-10.35	-34.49
84	39	1	106	5.9	2.7	28.06	3	3	24.88	2	3	-2.9	-49.15	0.3	11.11	-3.18	-11.33
85	16	1	83	3.3	0.7	159.6	0.2	0.9	119.64	0	3	-3.1	-93.94	0.2	28.57	-39.96	-25.04
86	24	1	133	2.7	1	96.61	0.16	0.8	126.23	0	3	-2.54	-94.07	-0.2	-20	29.62	30.66
87	28	2	100	2.6	4.8	11.46	.	7.1	7.3	2	3	.	.	2.3	47.92	-4.16	-36.3
88	39	1	97	1.5	3.7	19.5	2.2	6.2	10.77	1	3	0.7	46.67	2.5	67.57	-8.73	-44.77
89	51	2	116	2	3.4	15.11	0.39	2.8	18.93	1	3	-1.61	-80.5	-0.6	-17.65	3.82	25.28
90	59	2	113	0.9	1.4	40.84	0.49	1.1	54.03	0	3	-0.44	-47.31	-0.3	-21.43	13.19	32.3
91	43	1	107	5.8	3.1	23.45	4.8	2.6	28.78	2	3	-1	-17.24	-0.5	-16.13	5.33	22.73
92	46	1	127	4.3	10.8	5.47	0.069	1.1	76.6	2	3	-4.23	-98.4	-9.7	-89.81	71.13	1300.37
93	30	2	105	2.9	6.4	11	0.89	6.2	8.43	2	3	-2.01	-69.31	-0.2	-3.13	-2.57	-23.36
94	44	2	105	2.5	3.9	15	0.6	1	93.61	2	3	-1.9	-76	-2.9	-74.36	78.61	524.07
95	22	1	109	5.5	4.7	16.62	1.9	4.7	16.65	2	3	-3.6	-65.45	0	0	0.03	0.18
96	48	1	104	0.9	1.7	45.87	1.5	1.4	57.49	2	3	0.6	66.3	-0.3	-17.65	11.62	25.33
97	24	2	106	1.6	1.9	34.46	0.81	1.8	36.74	1	3	-0.79	-49.38	-0.1	-5.26	2.28	6.62
98	32	1	116	2.2	3.9	19.11	2.1	1.7	49.89	1	3	-0.1	-4.55	-2.2	-56.41	30.78	161.07
99	21	1	119	1.4	0.9	10.77	.	12.3	5.54	1	3	.	.	11.4	1266.67	-5.23	-48.56

100	31	1	111	2.1	2.3	38.28	0.4	1.9	44.17	1	3	-1.7	-80.95	-0.4	-17.39	5.89	15.39
101	37	1	97	4.6	1.7	48.36	0.78	1.2	72.41	1	3	-3.82	-83.04	-0.5	-29.41	24.05	49.73
102	38	2	110	1.6	1.2	85	1.4	1.3	48.72	0	3	-0.2	-12.5	0.1	8.33	-36.28	-42.68
103	35	1	113	4	1.7	48.91	0.95	2	40.61	0	3	-3.05	-76.25	0.3	17.65	-8.3	-16.97
104	45	1	117	1.8	2.3	32.79	0.38	2	38.59	0	3	-1.42	-78.89	-0.3	-13.04	5.8	17.69
105	27	1	120	2.2	3.6	21.53	1.3	9.8	6.8	2	3	-0.9	-40.91	6.2	172.22	-14.73	-68.42
106	19	2	100	4.2	2.7	30.23	2.8	0.8	98.21	2	3	-1.4	-33.33	-1.9	-70.37	67.98	224.88
107	15	1	86	1	1.4	59.56	0.76	1.4	72.8	1	3	-0.24	-24	0	0	13.24	22.23
108	47	1	124	3.5	2.8	25.79	0.248	4.7	14.27	2	3	-3.25	-92.91	1.9	67.86	-11.52	-44.67
109	26	1	124	5.3	3.1	26.18	3.2	3.6	20.65	2	3	-2.1	-39.62	0.5	16.13	-5.53	-21.12
110	35	1	131	4.4	5.2	13.46	.	7	9.57	1	3	.	.	1.8	34.62	-3.89	-28.9
111	23	1	89	0.1	1.7	53.26	2	1.9	46.92	1	3	1.88	1552.89	0.2	11.76	-6.34	-11.9
112	55	1	91	3.6	3.8	17.64	0.62	5.3	12.03	0	3	-2.98	-82.78	1.5	39.47	-5.61	-31.8
113	31	1	111	1.5	1.3	67.88	0.26	1.4	62.8	1	3	-1.24	-82.67	0.1	7.69	-5.08	-7.48

Results

RESULTS :

Baseline characteristics :

Table 1 summarizes the baseline details of the study population.

The sample size in 3 groups is 41, 31 and 41 respectively . Baseline characteristics reveal a predominantly younger population with a mean age of 34.5 years in MPA group ,34.3 and 34.4 in control groups respectively, the difference among the groups is not significant.

Sex distribution is favouring males with the ratio being 3.5:1 , 1.6:1 and 3.1:1 in the 3 groups .

Mean arterial blood pressure at baseline is 107.5 mm Hg , 104.9 and 108.9 mm Hg in the 3 groups.

Median 24 hour urine protein excretion is 2.3 gm,3.6 gm and 2.6 gm in the 3 groups.

Median serum creatinine is 2.2 mg%, 1.6 and 2.7 mg% in the groups.

Median e GFR is 33.3 , 48.9 and 29.5 ml/min/1.73m² BSA respectively in the MPA , steroid and no steroid group , the difference among MPA group and steroid group being significant.

Global sclerosis : The percentage of patients with global sclerosis is 61.1% ,22.6% and 34.1% respectively in MPA ,steroid and no steroid groups. The differences were statistically significant.

TABLE 1 – Baseline characteristics

<i>Variables</i>	<i>MPA</i>	<i>Steroid</i>	<i>No steroid</i>	<i>p</i>
<i>Age</i>	34.5 ± 7.6	34.3 ± 13.7	34.4 ± 12.6	MPA vs Ster:0.92 MPA vs No ster:0.949
<i>Sex(M:F)</i>	3.5:1	1.6:1	3.1:1	0.125 0.797
<i>MAP</i>	107.5 ± 14.5	104.9 ± 12.7	108.9 ± 11.5	0.43 0.65
<i>Proteinuria</i> (gm/24 hrs)†	2.3 (1.3 - 3.8)	3.6 (1.7 - 6.4)	2.6 (1.5 - 4.3)	0.049 0.728
<i>S.Creatinine</i> †	2.2 (1.9 - 2.8)	1.6 (1.1 - 3.0)	2.7 (1.6 - 3.8)	<u>0.021</u> 0.305
<i>eGFR</i> †	33.3 (26.4 - 42.3)	48.9 (20.9 - 76.6)	29.5 (19.3 - 48.7)	<u>0.038</u> 0.344
<i>Global sclerosis</i> no./(%)	22/61.1% (n=36)	7/22.6% (n=31)	14/34.1% (n=41)	<u>0.003</u> <u>0.023</u>

† - Median (25 – 75 th percentile)

Outcomes : Table 2

After 3 months of followup , outcomes depicted as percentage change were as follows.

Proteinuria –

MPA group – 58.8 % reduction in proteinuria when compared to baseline.

Steroid group – 45.3% reduction in proteinuria when compared to baseline .

No steroid group – 48.5% reduction in proteinuria when compared to baseline.

The changes in proteinuria were not statistically significant with the p values being 0.55 for MPA vs steroid group and 0.31 for MPA vs no steroid group.

TABLE 2 - Outcomes

<i>Variables</i>	<i>MPA</i>	<i>Steroid</i>	<i>No steroid</i>	<i>p</i>
<i>% change in proteinuria</i>	-58.8 (-83.5 to -35.1) (n=39)	-45.3 (-86.2 to -21.0) (n=29)	-48.5 (-81.1 to -12.5) (n=38)	MPA vs Ster :0.55 MPA vs No ster:0.31
<i>% change in eGFR</i>	16.9 (0.0 to 35.3) (n=41)	11.6 (-9.6 to 72.0) (n=31)	-8.2 (-28.6 to 24.9) (n=41)	0.58 <u>0.004</u>
<i>% change in S.Creatinine</i>	-12.5 (-2.3 to - 0.5) (n=41)	-9.1 (-29.4 to 9.1) (n=31)	7.7 (-17.5 to 31.6) (n=41)	0.50 <u>0.005</u>
<i>MAP mmHg(at 3 months)</i>	101.4 ± 11.5 (n=36)	100.1 ± 9.3 (n=14)	104.2 ± 11.0 (n=25)	0.67 0.34

Renal function :

There is 16.9 % improvement in e GFR after 3 months of treatment in MPA group when compared to baseline vs 11.6 % in steroid group although it is not statistically significant ($p = 0.58$). In the 'no steroid' group, there is 8.2% reduction in e GFR which is statistically significant when compared to MPA group ($p = 0.004$). Changes in serum creatinine showed similar trends which is given in table 2.

After 3 months of followup , wherever data is available , the mean blood pressure recordings in 3 groups is not significantly different (table 2).

Subgroup analysis :

ACE-I inhibitors :

Since variable number of patients in all 3 groups received ACE-I/ARB's , subgroup analyses is done to see the effect of ACE-I/ARB's. Number of patients in each group are as follows : MPA Group – 31

Steroid group – 17

No steroid group – 24

Baseline characteristics were given in table 3. As to baseline details regarding age, mean arterial pressure, proteinuria, serum creatinine and e GFR , there is no statistical significant difference between the groups.

Table 3 – Baseline characteristics among ACE-I subgroup

<i>Variables</i>	<i>MPA</i>	<i>Steroid</i>	<i>No steroid</i>	<i>p value</i>
<i>Age</i>	34.52±7.93	30.88±12.63	36.29±14.53	0.34
<i>MAP</i>	105.78±13.78	106.34±13.19	106.34±11.88	0.98
<i>Proteinuria(gm/24 hrs)†</i>	2.3 (1.20-3.80)	3.5 (1.65-6.15)	1.7 (1.05-3.52)	0.25
<i>S.Creatinine†</i>	2.0 (1.70-2.50)	1.6 (1.10-2.80)	1.7 (1.42-2.70)	0.213
<i>eGFR†</i>	37.40 (28.80-50.80)	58.86 (28.81-79.53)	47.15 (29.63-53.42)	0.224

† - Median (25 th to 75 th percentile)

Outcomes – Table 4

After 3 months of followup, there is 58.8 % reduction in proteinuria in MPA group whereas it is 35.1% and 47.6% in steroid and no steroid groups respectively. Regarding renal function, e GFR is better by 19.5%,11.6% and 3.25 in the 3 groups respectively and the difference reached statistical significance when MPA group is compared to no steroid group.

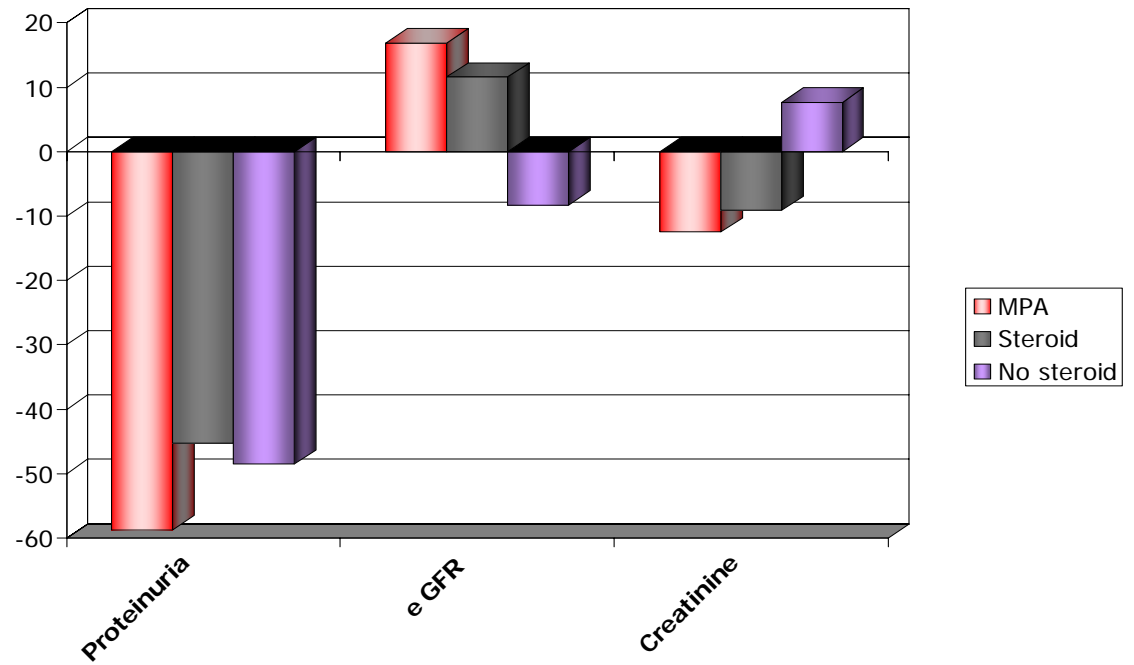
Table 4 – Outcomes among ACE-I subgroup

<i>Variables</i>	<i>MPA</i>	<i>Steroid</i>	<i>No steroid</i>	<i>p value</i>
% change in proteinuria	-58.83 (-87.03 to -37.85)	-35.16 (-85.10 to -5.33)	-47.61 (-81.24 to -12.39)	MPA vs steroid :0.258 MPA vs No steroid :0.18
% change in eGFR	19.53 (0.00 to 30.88)	11.63 (-21.07 to 72.01)	3.22 (-22.17 to 24.47)	0.787 <u>0.02</u>
% change in S.Creatinine	-14.29 (-20.83 to 0.00)	-9.09 (-37.50 to 27.65)	-2.63 (-17.27 to 24.47)	0.854 <u>0.02</u>

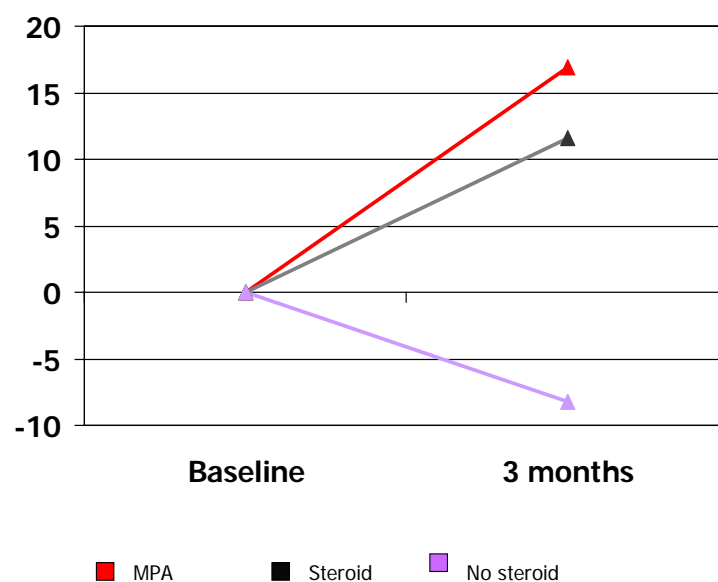
SIDE EFFECTS :

A total of 2 patients in MPA group had diarrhea which did not require drug discontinuation but only dose modification. 2 patients had pyoderma. Other patients tolerated the drug reasonably well without any significant side effects.

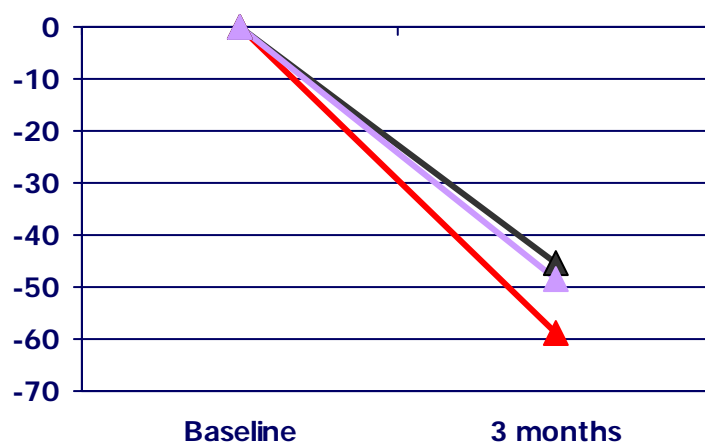
Outcomes



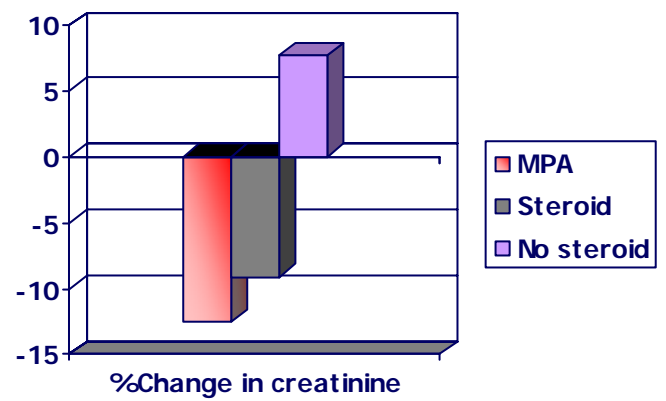
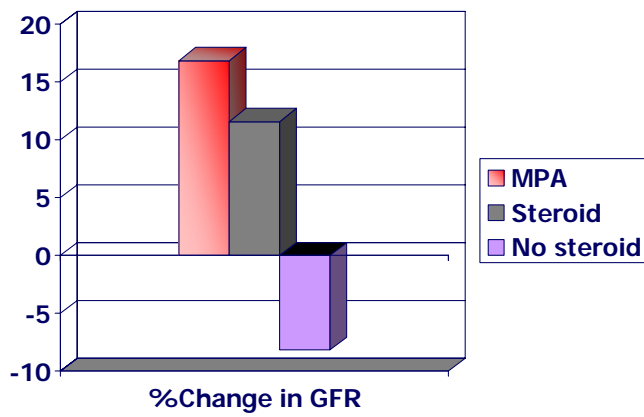
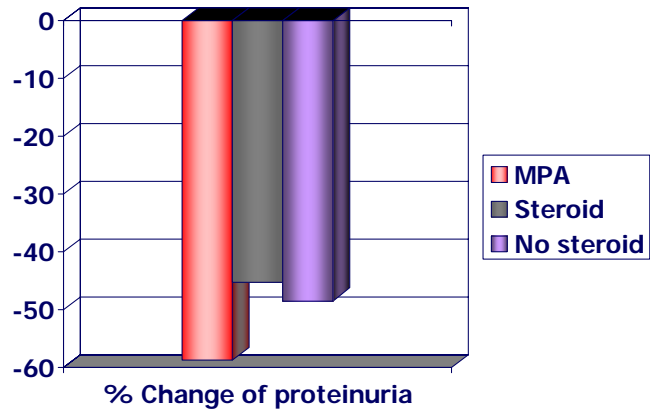
% Change in GFR



% Change in proteinuria



Outcomes



Discussion

IgA Nephropathy has a rapid progression in Indian population with renal survival of only 35% at 10 years after onset of symptoms whereas the survival was 80% in case of Caucasian population [160] . Trials to test therapies which slow the rate of progression are needed to tackle this common glomerulonephritis .

There are only a small number of trials using MMF in IgAN. Chen *et al.* compared the use of MMF 0.5–0.75 g twice daily with prednisone 30–40mg daily in 62 Chinese patients with IgAN (30 with >72 weeks follow-up) and showed a benefit with respect to serum creatinine and proteinuria [135] .

In 2005, Tang *et al* published a prospective study in 40 Chinese patients with IgAN and mild tubulointerstitial lesions who were randomized 1:1 to 1.5 (BW < 60 kg) or 2.0 g/day MMF for six months or continuation of contemporaneous medication only after blockade of the renin-angiotensin system failed to reduce proteinuria to < 1 g/d. Twelve months after stopping MMF, the overall remission rate (proteinuria < 0.3 g/d or 50% of baseline) was significantly higher in MMF-treated patients whose proteinuria dropped to 62% of baseline, whereas urine protein in control patients increased to 120% of baseline[137] .

Maes *et al.* randomized 34 IgAN patients in Belgium to either MMF 2 g daily or placebo. After 3 years of follow-up, no significant differences in serum creatinine or proteinuria were found, although the study probably lacks sufficient power [136].

Another study which took patients of Ig A Nephropathy with moderately advanced renal failure with a mean creatinine of 2.4 mg% and assessed the role of 1 year of MMF treatment was prematurely terminated because the interim analysis done by the independent study monitor revealed a trend towards a worse outcome in the MMF group

that would have made it very unlikely eventually to show a benefit for MMF given their rate of recruitment and their target sample size [138] .

Our study shows that in primary IgA Nephropathy patients at high risk of progression, treatment with mycophenolic acid in addition to steroids and antihypertensives led to a significant improvement in renal function when compared to antihypertensives alone and a trend towards better renal function is observed when compared to steroids plus antihypertensives. With regard to proteinuria, there is no significant difference with MPA treatment when compared to other 2 groups .

We took a population of IgAN with a fairly advanced disease as shown by the high mean serum creatinine of 2.2 mg% (vs creatinine of 1.6 mg% in the steroid group) and presence of global sclerosis in 61.1 % of the study population in the MPA group (vs 22.6% and 34.4% in steroid and no steroid groups respectively) which was much higher than steroid group. Although to start with, renal function was worse in the MPA treatment arm with significant chronicity, at the end of follow up, there was a 16.9% improvement in e GFR and this was higher than the 11.6 % increase in steroid group although this did not reach statistical significance. A small sample size may have precluded statistical significance. However , the increase was statistically significant when compared to the ‘no steroid’ group.

Our results are at variance with previous studies [136,138] which showed that MPA was not beneficial in Ig A Nephropathy. Previous studies suggest that MMF is efficacious in Chinese population whereas at the same time, MMF is documented to be of no use in Caucasian population. Whether this variability in response depending on the ethnicity

explains partly the encouraging response in our Indian population is highly speculative. This needs to be studied further.

Certain factors in our study need to be considered . The small sample size of our study may have precluded definite conclusions. Short followup duration says that these results were only suggestive of a benefit and further randomized studies with a large sample size and long term followup need to be planned.

The results could have been influenced by the fact that variable number of patients received ACE-I/ARB's in the 3 groups. Hence, a subgroup analysis was done among those patients who received ACE-I/ARB's in the 3 groups. The results showed a similar trend as that of entire cohort and this goes on to say that the benefit achieved in MPA group is not due to ACE-I/ARB's alone.

Most of our patients tolerated MPA. 2 patients had diarrhea which required dose modification and another 2 had pyoderma. None of them were discontinued on MPA.

Based on the encouraging results in this case-control study, a randomized study comparing steroids in 1 arm to mycophenolic acid and steroids in other arm along with ACE-I(in both arms) and with a follow up of atleast 5 years would give further insight as to the role of MPA.

Conclusions

CONCLUSIONS :

1. In high risk primary IgA Nephropathy ,
 - Combination of mycophenolic acid with steroids and antihypertensives led to a significant improvement in renal function when compared to antihypertensives alone and
 - there was a trend towards better renal function when compared to steroids with antihypertensives.
2. With regard to proteinuria, there is no significant difference with mycophenolic acid treatment when compared to antihypertensives with or without steroids.
3. Whether ethnicity variation in response to mycophenolic acid favours Indian population needs to be studied.
4. Mycophenolic acid is well tolerated in our population with acceptable side effects.
5. Randomized controlled trials in this area of clinical research are urgently needed.

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